ARCHIVES OF SURGERY

VOLUME 46 APRIL 1943 NUMBER 4

COPYRIGHT, 1943, BY THE AMERICAN MEDICAL ASSOCIATION

EFFECTS OF JEJUNAL TRANSPLANTS ON EXPERIMENTAL PRODUCTION OF PEPTIC ULCERS

JERE W. LORD JR., M.D.

WILLIAM DEW. ANDRUS, M.D.

AND

PAUL STEFKO

NEW YORK

Stefko, Andrus and Lord [1] recently described the effects on the gastric secretion of transplantation to the stomach of a segment of jejunum with intact blood supply. Briefly, they observed that in 5 animals subjected to this procedure the normal response of increased acidity after injection of histamine was reversed in 4 and markedly reduced in the fifth, as demonstrated by direct measurements of the p_H of the gastric mucosa of seven regions of the stomach. This same reversal was also strikingly evident in the analyses of the gastric contents, which showed a reduction of the average fasting free and combined acidities after jejunal transplantation, followed by a still further decrease after the injection of histamine.

The present paper deals with the effects of such jejunal transplants on experimental production of peptic ulcers of the duodenum through daily intramuscular injection of a mixture of histamine phosphate and beeswax in liquid petrolatum as reported by Varco and his associates.[2] These authors attributed such ulcers to "the continuous excessive secretion of acid gastric juice evoked by the histamine in the beeswax mixture." In view of the effects of the jejunal transplants in normal animals when the usual amount of histamine phosphate (1 mg.) was injected for gastric analysis, it was felt desirable to investigate the effects during more prolonged exposure to the drug. To this end two series of experiments were carried out.

EXPERIMENTS

In the first series, 2 control dogs and 2 dogs in which a jejunal segment with intact blood supply had been implanted into the stomach about two and a half months previously received intramuscular injections of a mixture of histamine and beeswax equivalent to 120 mg. of histamine phosphate daily, except for Sunday, for a period of thirty days. At the end of the thirty day period gastric analyses

This study was carried out under a grant from the John and Mary R. Markle Foundation.

From the Department of Surgery of the New York Hospital and Cornell University Medical College.

1. Stefko, P.; Andrus, W. DeW., and Lord, J. W., Jr.: Effects of Jejunal Transplants on Gastric Acidity, Science **96**:208 (Aug. 28) 1942.

2. These authors (Varco, R. L.; Code, L. F.; Walpole, S. H., and Wangensteen, O. H.: Duodenal Ulcer Formation in the Dog by Intramuscular Injections of a Histamine Beeswax Mixture, Am. J. Physiol. **133**:P475 [June] 1941) described the preparation as follows: "The histamine beeswax mixture was prepared by mixing finely ground histamine with one part hot beeswax and then diluting with four to five parts hot mineral oil. When homogeneous and while still molten, the mixture was drawn into a 1 cc. tuberculin syringe and allowed to solidify at room temperature."

were carried out, after which all 4 were killed and the gastrointestinal tract carefully examined. Results of gastric analyses performed at the end of the experimental period for these 4 animals appear in the accompanying table.

Results of Gastric Analyses of Animals in First Series

		Fasting	10 Minutes After Injection	20 Minutes After Injection
Dog 1 (transplant)	Free	30	28	18
	Combined	30	24	22
	Total	60	52	40
Dog 2 (transplant)	Free	50	40	0
	Combined	38	32	25
	Total	88	72	25
Dog 3 (control)	Free	70	70	102
	Combined	40	50	40
	Total	110	120	142
Dog 4 (control)	Free	70	74	90
	Combined	38	40	30
	Total	108	114	120

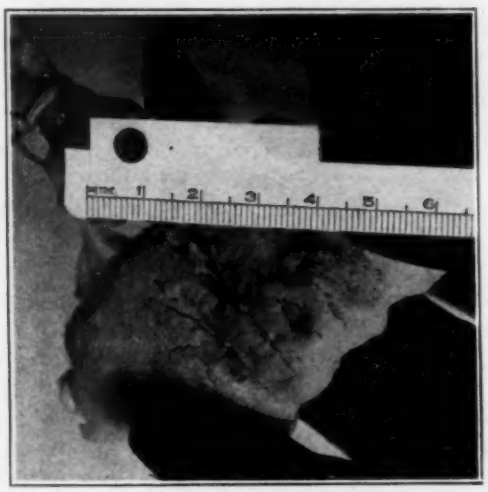


Fig. 1.—Erosion, 11 by 6 mm., in the first portion of the duodenum of dog 3.

Several facts are to be noted. First, the fasting free acidity was much lower in the experimental than in the control animals despite the prolonged exposure to histamine. Also, the previously noted reversal of the normal response of increased acidity ten and twenty minutes after injection of histamine was seen in these animals.

The observations at autopsy were as follows: Dog 3 had multiple erosions, both small and large (diameter of 4 to 11 mm.), in the first and second parts of the duodenum. Some of the erosions had penetrated to the submucosa, and the surrounding mucosa was hyperemic. The stomach was entirely normal (fig. 1). Dog 4 had multiple superficial punctate erosions in the first and second portions of the duodenum, and the mucosa of the pylorus and duodenum was hyperemic. Otherwise the organs of the animal were entirely normal.

On the other hand, careful examination of the duodenum and the remainder of the gastrointestinal tract of the 2 dogs with jejunal transplants failed to reveal any pathologic abnormality. The jejunal transplant in each dog had healed well and appeared unremarkable.

While the results in the first series of animals appeared highly suggestive so far as the action of a jejunal transplant in preventing duodenal ulceration following

prolonged exposure to histamine was concerned, it seemed desirable to pursue the matter further and, if possible, observe the effect of the operation in the presence of duodenal ulceration. A second series of animals was therefore investigated, consisting of 6 normal dogs and 1 with a jejunal transplant in the stomach. All were given injections of the mixture of histamine and beeswax equivalent to 120

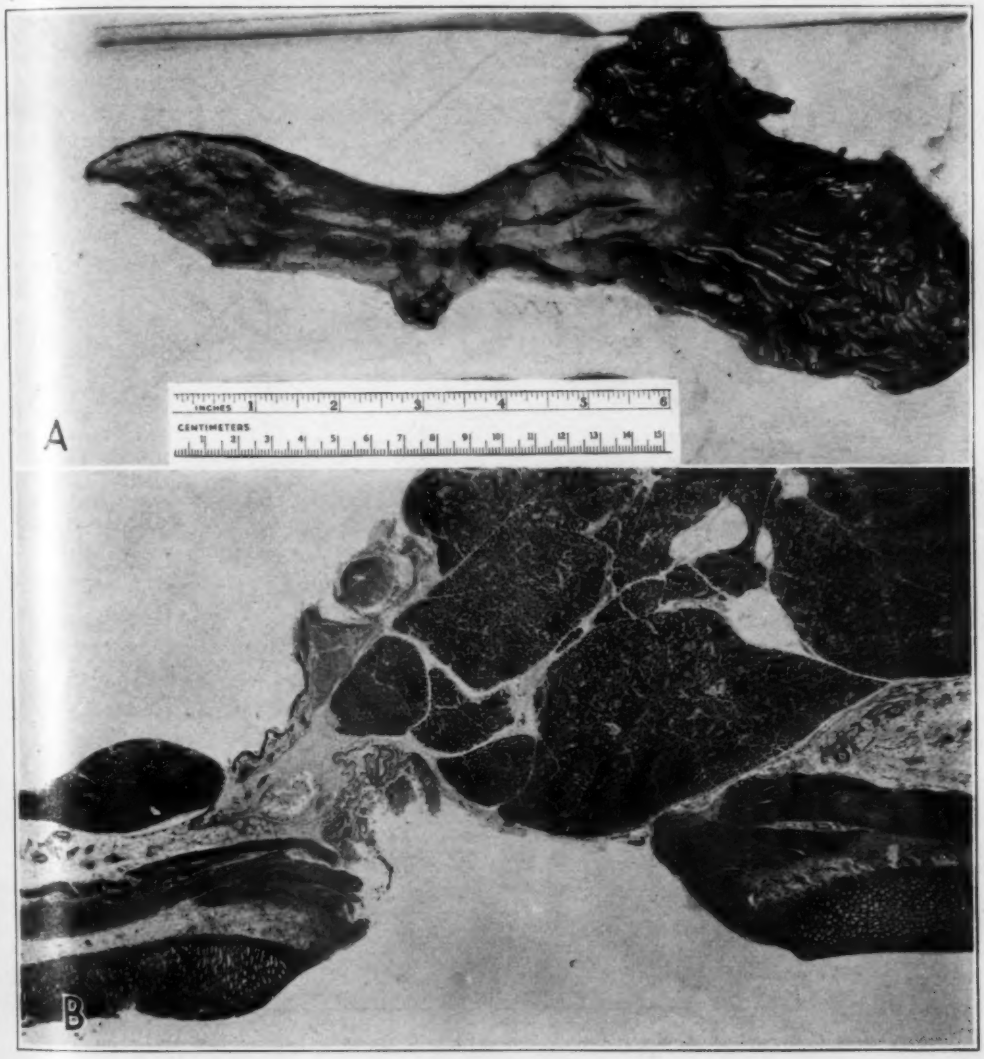


Fig. 2.—*A*, part of the stomach and duodenum of dog 5, showing two large penetrating ulcers in the first and second portions of the duodenum and several erosions through the mucosa of the antrum. *B*, low power photomicrograph of a cross section of the ulcer in the second portion of the duodenum. Complete destruction of the entire wall of the duodenum has occurred, with the pancreas forming the greater portion of the base of the ulcer. Two good-sized vessels can be seen in the base of the ulcer.

mg. of histamine phosphate daily for a period of seven weeks. The animal with the jejunal transplant was observed for the entire period and was then killed while in a state of good health. The others were examined at various times during the experiment when they appeared ill.

In all 6 of the previously normal animals hyperemia and lesions of the duodenal mucosa developed at some time during the experimental period. In 3 definite duodenal ulcerations extending into the muscularis were found, while in the remainder multiple mucosal erosions were to be seen. All suffered from anorexia and lost weight, and several had definitely tarry stools.

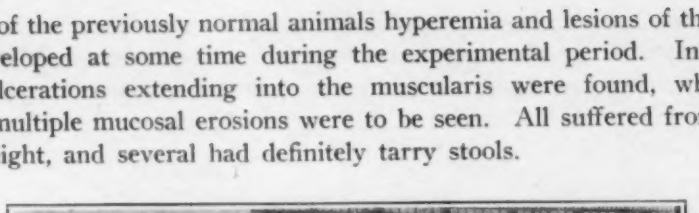


Fig. 3.—Part of the stomach and duodenum of dog 6. The jejunal transplant can be seen in the center of the stomach. The mucosa of the stomach and duodenum is entirely free from erosions and ulcers.

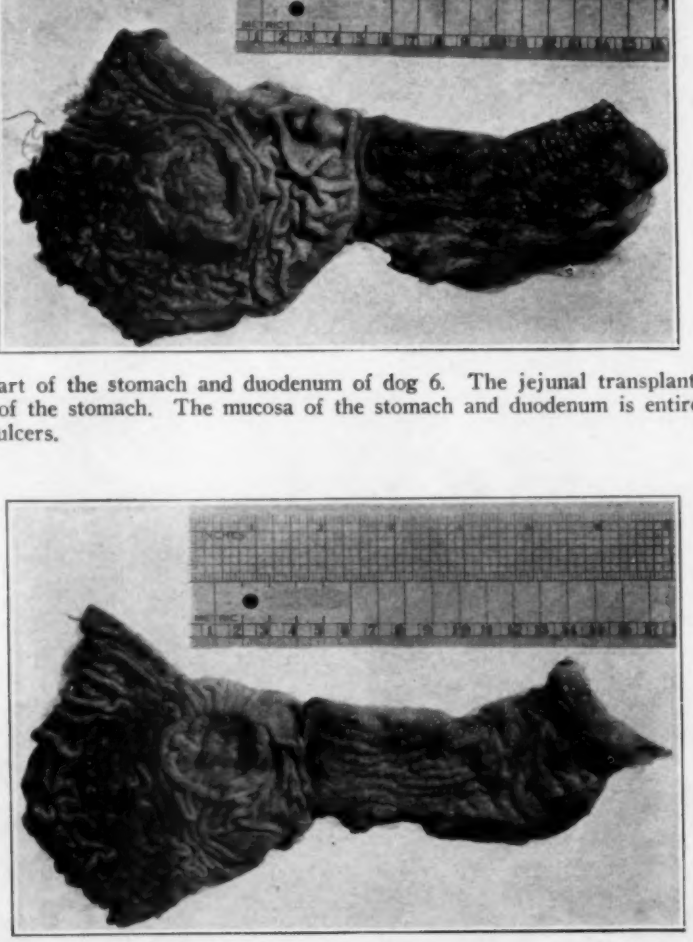


Fig. 4.—Part of the stomach and duodenum of dog 7, showing normal mucosal lining. The jejunal transplant can be seen near the pylorus.

The course of dog 5 was typical of that in the 3 control dogs in which ulcers developed during the experiment. This dog began to lose appetite and weight on the ninth day after the injections of the mixture of histamine and beeswax were begun (July 6, 1942) and continued to do poorly for two weeks, when it began to improve, ate all of its food and put on weight. On August 5 the routine was changed slightly, the injection of the mixture being made in the late afternoon instead of in the morning when the dogs were fed. The next day the dog began to vomit its food. During the next four days it went rapidly downhill, refusing

to eat and vomiting, and finally it began wheezing and died on the thirty-fifth day of the experiment, five days after the change in the time of the injection of the mixture. The animal lost 8 pounds (3.6 Kg.) in weight during the entire period of thirty-five days. Autopsy showed two large, deep ulcers in the first and second parts of the duodenum. Also, there were multiple erosions of the mucosa of the stomach and duodenum associated with hyperemia (fig. 2). Several ounces of bloody fluid was in the stomach. Both lungs were the seat of a bronchopneumonia of a moderate degree.

In contrast, the dog with the jejunal transplant (dog 6) tolerated the prolonged exposure to histamine extremely well, remaining in excellent health throughout the experiment. At autopsy its stomach and duodenum appeared entirely normal (fig. 3).

Two animals were operated on while acutely ill, with the idea of establishing the presence of duodenal ulceration by direct examination and then, after implanting a segment of jejunum in the stomach, observing its effect during continued exposure to histamine. One of these animals died twenty-four hours later with confluent bronchopneumonia, but the other recovered promptly from the operation. This animal, dog 7, had become ill shortly after the onset of the experiment. Tarry stools were noted on the eighth day, and anorexia became complete during the next four days, associated with a moderate decrease in weight (from 26 to 24 pounds [11.8 to 10.9 Kg.]). On the twelfth day a duodenotomy and a jejunal transplant to the stomach were carried out. Several punctate erosions of the duodenal mucosa were seen. The stomach contained some gastric juice, which on testing showed free acidity of 80 degrees and combined acidity of 50 degrees, a total of 130 degrees. No frank ulcer could be palpated or seen through the duodenotomy incision or the window in the anterior wall of the antrum prior to the implantation of the jejunal segment. Postoperatively, the daily injection of the mixture of histamine and beeswax was continued for the remaining twenty-six days of the experiment. No food or water was administered for forty-eight hours, infusions of dextrose and saline solution having been given on the operative day and for the next two days. On the third postoperative day the dog was allowed water by mouth, and shortly thereafter it was given milk and bread. For the last two weeks of the experiment the animal was fed only chopped meat. Immediately postoperatively its condition improved, and it ate everything given it without incident for the duration of the experiment and gained 4 pounds (1.8 Kg.) in weight. A gastric analysis on the tenth postoperative day showed the following values:

	Fasting	10 Minutes After Injection	20 Minutes After Injection
Free acid	34	32	20
Combined acid	28	28	24
Total	62	60	44

The animal was killed on the twenty-sixth postoperative day, and at autopsy the mucosa of the stomach and duodenum was entirely normal. The transplant had healed cleanly, and its mucosa was intact. The duodenotomy incision had been closed satisfactorily without narrowing the lumen (fig. 4).

SUMMARY

The previous observation [1] that dogs with pedicle grafts of jejunum transplanted into the stomach wall secrete a gastric juice which becomes relatively more alkaline in response to histamine, in contrast to the normal reaction, has been confirmed in animals given larger doses of the drug for a relatively long period.

The results suggest efficacy of such transplants in preventing development of duodenal erosions and ulceration during continued exposure to histamine.

In the single animal in which it could be satisfactorily carried out, implantation of a pedicle graft of jejunum into the gastric wall was followed by healing of the duodenal lesions despite continuation of the injections of histamine.

The clinical application of transplantation of a jejunal segment with intact blood supply to the stomach in the treatment of peptic ulcer is suggested by these results. Further experimental work is in progress in an attempt to elucidate the mode of action of such a transplant and to establish its possible limitations. Such grafts have been shown [3] to remain viable for long periods, provided their blood supply is intact, and we have observed animals in which the operation has been performed up to two and a half years before, during which time they have remained in excellent health despite other operative procedures.

525 East Sixty-Eighth Street.

3. Dragstedt, L. R., and Vaughn, A. M.: Gastric Ulcer Studies, Arch. Surg. **8**:791 (May) 1924.

HEMANGIOMA OF JOINTS

CAPTAIN MILTON C. COBEY
MEDICAL CORPS, ARMY OF THE UNITED STATES

In 1939 Dr. George Bennett and I [1] reviewed the 24 reported cases of hemangioma of the knee joint, and in adding 5 more proposed the use of roentgen therapy for tumors of the nonpedunculated type. Attempts at radical excision had proved unsatisfactory for this type of hemangioma.

The purpose of this paper is to present 4 more cases of hemangioma of the knee joint and to bring out the fact that this tumor is not so rare that it should not be considered as a possibility in any differential diagnosis of swelling of the knee joint. Too often the diagnosis of early tuberculosis of the synovial membrane of the joint or of some minor injury to the joint is made. In many instances the cardinal signs of a family history of hemangioma, hemangiomas elsewhere on the patient's body, intermittent attacks of swelling and reduction of the size of the swelling of the knee on elevation of the extremity will make the diagnosis clear

In 1 of the following 4 cases the patient was treated by excision of a pedunculated tumor. Roentgen therapy was employed in the other 3 after the diagnosis had been established by biopsy and the lesion had been found to be too extensive for surgical excision.

REPORT OF CASES

CASE 1.—*Synovial Hemangioma.*

V. K., an 11 year old girl, was admitted to the Children's Hospital Orthopedic Dispensary, Washington, D. C., in December 1939 because of a swollen right knee of several months' duration. No other symptoms or signs were noted at the time of admission. The condition was diagnosed as a possible epiphysitis of the tibial tubercle, and a cast was applied. After three months in the cast the joint was still swollen. Aspiration was done, and guinea pigs were inoculated with the fluid obtained. The fluid was not blood, and laboratory tests gave negative results. The second cast was removed after two months, and physical therapy was instituted. The swelling of the joint persisted, although at certain times it was more swollen than at others. Ten months after the patient's first visit to the clinic a biopsy of the synovial membrane of the joint was performed, and the lesion proved to be a hemangioma. Roentgen therapy was started, and four months later the knee was apparently entirely well. The results of a careful two year follow-up indicate that it has remained so.

CASE 2.—*Pedunculated Tumor.*

R. H., a Negro woman aged 23, was first seen at the Garfield Hospital, Washington, D. C., on Feb. 20, 1941, and gave a history of having had pain and stiffness in her left knee for a period of a year. About three weeks before the onset of the pain the patient had fallen, but she could not recall injuring the knee at that time and had no pain in it afterward. She noticed that the pain and swelling had been definitely intermittent in type. At times they were so severe she was unable to extend the leg fully. There was no family history of hemangioma, and none was found on the patient at physical examination. The first examination revealed definite swelling and slight increase in synovial fluid but no definite capsular thickening. Except for generalized obesity there were no other physical signs. Roentgen

---

Released for publication by the War Department Manuscript Board, which assumes no responsibility, other than censorship, for the contents of the article.

1. Bennett, G. E., and Cobey, M. C.: Hemangioma of Joints, Arch. Surg. **28**:487-500 (March) 1939.

examination gave negative results. The preoperative diagnosis was tumor of the left knee. At operation a pedunculated hemangioma was found extending from the synovial membrane posteriorly between the cruciate ligaments out into the anterior portion of the joint. The pedicle was ligated, and the tumor was excised. The patient was given physical therapy postoperatively from March 11 to May 22. She was followed closely for one year after the termination of treatment and at the time of the last examination was apparently entirely well.

CASE 3.—*Synovial Tumor; Hemangioma in Other Members of the Family.*

B. M., a white girl aged 4 years, was brought to my office on May 15, 1941, with the complaint of swelling of the right knee and limping for six weeks. The joint was swollen throughout and felt doughy on palpation. There was a definite decrease in the amount of swelling of the joint on elevation of the extremity. On the left leg there was an extensive

Fig. 1 (case 3).—Low power photomicrograph showing a section from a hemangioma of the knee joint.

bluish discoloration of the skin from dilated subcutaneous vessels. The patient's younger sister had a hemangioma of the face; a paternal aunt had an extensive hemangioma of the deltoid muscle, and a paternal first cousin had a very large hemangioma of the scalp. Roentgen examination of the patient's knee showed numerous small phleboliths in the vessels of the capsule of the joint. Biopsy showed the tumor mass involving the capsule of the joint and the synovial membrane to be a hemangioendothelioma. The patient was not given roentgen therapy until one year after the diagnosis was made, because the parents at first refused to permit treatment. She then had a full course which resulted in prompt improvement. Examination one year after roentgen therapy showed the knee to be apparently entirely well.

CASE 4.—*Synovial Tumor Erroneously Diagnosed as Tuberculosis and Treated with Cast for Eight Years.*

I. S., a white girl aged 10 years, was admitted to the Orthopedic Dispensary of the Children's Hospital, Washington, D. C., on March 24, 1942, with a history of intermittent pain

and swelling in the right knee with a limp on walking since she was 18 months of age. She had spent most of the intervening time in casts and had been in and out of several tuberculosis sanatoriums, being treated for supposed tuberculosis of the knee joint. On examination there was 1.5 cm. overgrowth in length of the right leg and some atrophy of the muscle of the thigh. The capsule of the joint was definitely thickened on palpation, and the swelling decreased on elevation of the extremity and increased when it was placed in a dependent position. Examination of tissue removed for biopsy indicated the presence of a hemangioepithelioma. Roentgen therapy was begun, and in six weeks the swelling had decreased, and the symptoms were relieved when I examined her just before my enlistment in the Army.

Photomicrographs of sections from the lesions in cases 3 and 4 are characteristic of hemangioma (figs. 1 and 2). Many of the blood vessels are thin walled

Fig. 2 (case 4).—High power photomicrograph showing a section from a hemangioma of the knee joint.

and are sharply defined. The walls of other blood vessels are continuous with broad plaques of endothelial cells, which are of uniform structure. Throughout these sections extensive and dense plasma cell infiltration and some fibrosis are present.

The historical background and the pertinent literature were thoroughly reviewed in a previously published paper.[1] The admitted ease of error in diagnosis was also discussed. However, hemangioma of the joints is more common, I believe, than is generally appreciated. A number of factors make it possible to suspect this tumor if not always to diagnose it before exploration. A history of hemangioma in other members of the family, the finding of hemangioma in other parts of the

body, a history of intermittent swelling over a long period of time, a decrease in the swelling on elevation of the extremity or the absence of any other positive findings in an apparently healthy patient should suggest a diagnosis of hemangioma. Aspiration as a diagnostic procedure is of little value, I believe; for unless one tears vessels with the needle or luckily happens to plunge it directly into the tumor one will aspirate normal synovial fluid.

CONCLUSION

I have presented 4 more cases of hemangioma of the knee joint in order to demonstrate that this tumor occurs more commonly than is often appreciated.

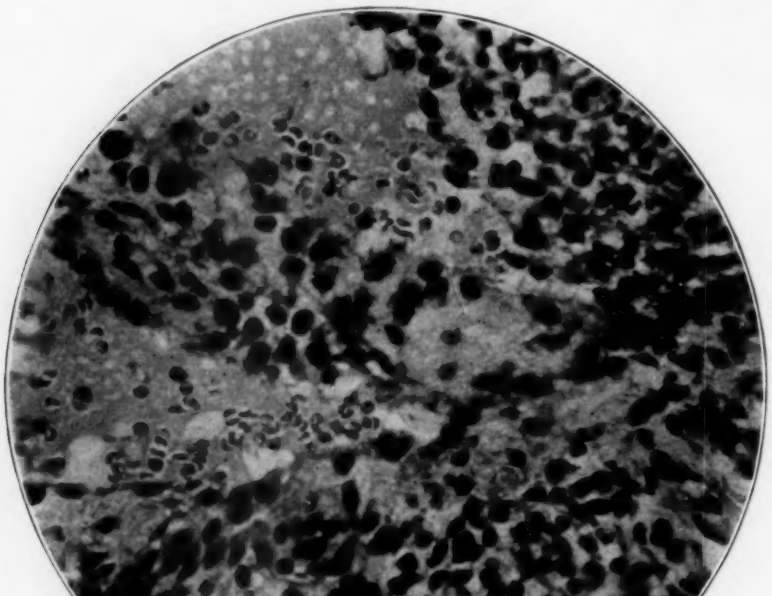


Fig. 3 (case 4).—Low power photomicrograph showing a section from a hemangioma of the knee joint.

to point out how easy it is to mistake the tumor for any one of a number of conditions that affect the knee joint and to reiterate the cardinal points in diagnosis.

The treatment is excision for pedunculated tumors and roentgen therapy for extensive lesions involving the synovial membrane and the capsule. The roentgen therapy usually requires about one week. The patient, however, should not be allowed to bear weight on the affected limb for three months after treatment is discontinued. This precaution should be taken because roentgen therapy may do damage to the growing epiphyses in a child. This risk, however, is not great.

POST-TRAUMATIC DYSTROPHY OF THE EXTREMITIES

A CHRONIC VASODILATOR MECHANISM

GÉZA DE TAKÁTS, M.D.
AND
DONALD S. MILLER, M.D.
CHICAGO

In 1900 Sudeck described puzzling vasomotor phenomena following comparatively mild injuries occurring mainly at the wrist or ankle.[1] Since his original communication, a variety of terms have been employed to characterize the same syndrome, such as traumatic angiospasm, chronic traumatic edema, acute atrophy of bone, post-traumatic osteoporosis, peripheral trophoneurosis and reflex nervous dystrophy. One of us summarized the literature and added a few cases in a previous communication.[2] Obviously, previous authors have focused their attention on different manifestations of the same syndrome as it affects the bone, the blood vessels or the skin. While Sudeck's name is rightfully associated with this condition, he himself preferred to omit his name in subsequent communications[3]; atrophy is not a typical feature of the disease in its early stages.

In this report we wish to give a brief summary of our observations on this vaguely understood and frequently unrecognized syndrome. Thirty-three patients have been studied and treated; 12 of these have had repeated plethysmographic studies made and other observations relating to blood flow, vasomotor reactivity and calcium metabolism.

REQUIREMENTS FOR EARLY DIAGNOSIS

In studying the published reports and our own series we find that severe, persistent pain of a burning character with paroxysmal aggravations presented by a patient whose injured limb is properly immobilized, noninfected and seemingly on the way toward a normal course of repair should make one suspicious of an early beginning reflex dystrophy. In this early stage the extremity is warm, the subcutaneous tissue and especially the periarticular spaces are edematous and the muscles are hypertonic in their effort to splint the painful joint. The cutaneous temperature is definitely elevated compared with that of the nonaffected extremity, and the oscillations are higher. At this stage the pain is closely limited to the site of injury and its spreading character is not evident; nor is there any osteoporosis, which does not seem to occur unless hyperemia has been present continuously for from four to eight weeks.

The syndrome may stop at this point or progress to a second stage. Here the periarticular edema has spread for a considerable distance; the part is not as warm and flushed and may become hard, cyanotic and cold to touch. Because of

From the Department of Surgery, the Graduate School, and the Research and Educational Hospital, University of Illinois College of Medicine.

1. Sudeck, P.: Ueber die acute entzündliche Knochenatrophie, Arch. f. klin. Chir. **62**: 147, 1900.

2. de Takáts, G.: Reflex Dystrophy of the Extremities, Arch. Surg. **34**:939 (May) 1937.

3. Sudeck, P.: Die trophische Extremitätenstörung durch periphere (infektiöse und traumatische) Reize, Deutsche Ztschr. f. Chir. **234**:596, 1931; Die kollateralen Entzündungsreaktionen an den Gliedmassen (sog. akute Knochenatrophie), Arch. f. klin. Chir. **191**:110, 1938.

the splinting action of the muscles and because of the synovial edema, the joints become stiff rather early, and this is one of the important residual disabilities with which one has to deal. Rheumatoid arthritis with its vascular phenomena is quite analogous to this condition. At this stage the pain is that of a spreading neuralgia.

Finally the skin becomes atrophic, the fingers or other joints are stiff, the muscles are atrophic and evidence of osteoporosis appears in the roentgenograms. There is a spotty decalcification of the small bones of the hand and foot and in the metaphyses of long bones, where vascularity is the greatest. There can be no doubt that the cause of this decalcification is hyperemia.[4] The mottled, spotty osseous atrophy later becomes diffuse, at which time it is indistinguishable from osteoporosis of other origin, such as that due to inactivity, senility, undernutrition or biliary fistula. We doubt that the diagnosis of Sudeck's atrophy can ever be made on the basis of roentgenograms alone. The syndrome may be present in the absence of osteoporosis, or it may be subsiding when the bony changes are at their height. The pain does not follow the course of osteoporosis, because after sympathectomy the pain may rapidly subside but the osteoporosis persists for many months. The greatest value of roentgenograms lies in serial examinations. When coarse trabeculation occurs with evidence of recalcification the peak of disability has passed. Complete restitution of osseous structure has not been seen in our roentgenograms.

DIFFERENTIAL DIAGNOSIS

The syndrome of Sudeck's atrophy may be so vague at first and clouded by such additional complications later that its differentiation from other conditions is not always easy. Elsewhere[5] we have discussed the point that reflex dystrophy is often associated with syndromes from which some authors try to separate it. Thus we are convinced that in this syndrome the early spotty osseous atrophy caused by increased blood flow to the bone is complicated later by a superimposed atrophy of disuse. Atrophy of bone seen around tuberculous or rheumatic joints must be recognized, but it may well be, as we shall point out, that this atrophy is caused by the same vasodilator mechanism which operates in the traumatic cases. Aseptic necrosis of bone causes rarefaction, but the roentgenograms do not show the ground glass appearance of Sudeck's atrophy. Senile osteoporosis is most evident in the vertebrae but may involve other parts of the skeletal system. In 3 of our cases the presence of senile osteoporosis of the spine seemed to aggravate local post-traumatic osteoporosis and make it less responsive to treatment. Other forms of osteoporosis due to hyperparathyroidism, hyperthyroidism, pituitary basophilism and adrenocortical syndromes, metastatic malignant lesions, multiple myeloma and osteomalacia have been discussed and differentiated from senile osteoporosis by Black, Ghormley and Camp.[6] They can hardly be confused with Sudeck's atrophy.

Finally, traumatic neurosis, compensation neurosis and malingering may have to be considered. It is here that the definite vascular changes to be described are of value. But it must be pointed out that the anxiety state of he patient may have a bearing on his autonomic reflexes and that from the standpoint of therapy all disturbing cortical and subcortical influences should be eliminated by early

4. Pommer, G.: Ueber Osteoporose, ihren Ursprung und ihre differentialdiagnostische Bedeutung, Arch. f. klin. Chir. **136**:1, 1925.

5. Miller, D. S., and de Takáts, G.: Post-Traumatic Dystrophy of the Extremities, Surg., Gynec. & Obst. **75**:558, 1942.

6. Black, J. R.; Ghormley, R. K., and Camp, J. D.: Senile Osteoporosis of the Spinal Column, J. A. M. A. **117**:2144 (Dec. 20) 1941.

settlements, reassurance and relief from anxiety. Again it is our feeling that instead of trying to differentiate Sudeck's atrophy from a "state of mind" the participation of this element should be ascertained, since it probably plays a role in the symptoms of injury.

The hard, traumatic edema produced artificially by a constricting band may be recognized by obtaining an infra-red picture of the suspected site of constriction, since it shows subcapillary extravasations in the form of a band.

STUDIES ON BLOOD FLOW IN REFLEX DYSTROPHY

One of us (D. S. M.) slightly modified the excellent water plethysmograph described by Abrahamson,[7] and all readings were carried out with this apparatus. The apparatus can be used for arm, hand or foot (fig. 1) and has been described in detail elsewhere.[5] The patients came to the laboratory early in the morning without breakfast. They were placed comfortably on a bed and rested for thirty

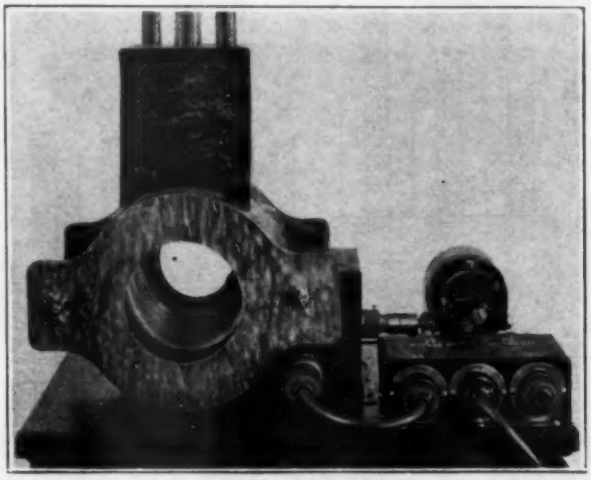


Fig. 1.—Final design of plethysmograph, the result of several modifications. The apparatus may be used for hand or foot; the temperature of the water bath is thermostatically controlled.

TABLE 1.—*Studies of Blood Flow in Post-Traumatic Reflex Dystrophy*

Case	Number of Studies	Blood Flow in Cc. per 100 Cc. of Limb Volume		Limb Volume in Cc.		Percentual Increase of Blood Flow in Affected Limb
		Affected Limb	Normal Limb	Affected Limb	Normal Limb	
1. R. H.	13	5.85	4.84	444	432	+20
2. S. O.	10	4	2.84	1,013	934	+39
3. F. O.	6	3.41	2.55	975	930	+33
4. K. W.	6	1.9	1.43	800	806	+35
5. M. B.	12	1.58	1.50	838	708	+ 5
6. B. S.	13	6.07	5.11	240	270	+18
7. C. B.	4	1	1.23	887	806	—23
8. R. D.	8	3.7	1.8	916	849	+48.6
9. E. L.	9	7.4	5.92	258	282	+25
10. B. M.	10	5.86	4.60	463	463	+29
11. M. Y.	11	4.49	2.80	878	826	+60
12. G. D.	12	5.12	4	985	881	+27
Total.....	114	45.26	38.42	8,707	8,427	+30.3

7. Abrahamson, D. I.; Zazeela, H., and Marrus, J.: Plethysmographic Studies of Peripheral Blood Flow in Man: I. Criteria for Obtaining Accurate Plethysmographic Data, Am. Heart J. **17**:194, 1939.

minutes covered with a light woolen blanket. The temperature of the water bath in which the extremity was placed was 32 C. (89.6 F.) except in some instances, in which cool or hot environmental effects were studied. The results were calculated in cubic centimeters of blood per hundred cubic centimeters of limb volume. From 6 to 20 trials were made on each extremity and the average taken from them.

A total of 114 determinations were made on the injured extremities and the same number on the normal extremities of 12 patients. Table 1 shows a summary of our findings. In 11 of the 12 patients the affected limb showed an increase in blood flow, varying from 60 per cent to 5 per cent. The volume of the affected limb was also usually larger, although the increase in volume did not parallel the increase in blood flow. The patient in case 7 showed a very small basal blood flow with a low basal metabolic rate and showed an even smaller blood flow in the affected limb. As a subsequent sympathectomy revealed, there was

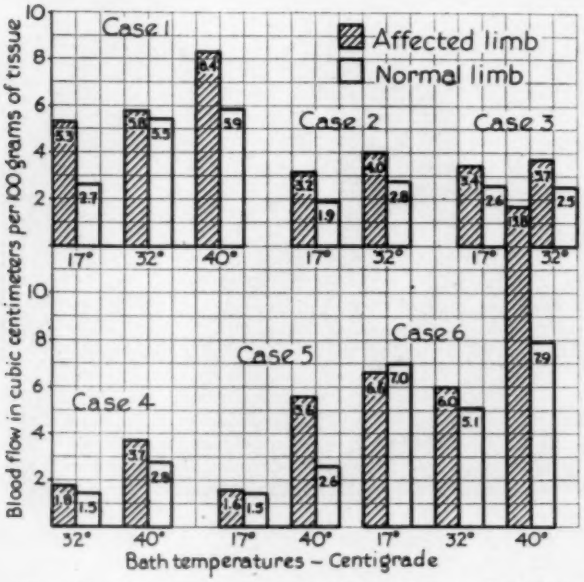


Fig. 2.—The effect of temperature on blood flow in Sudeck's atrophy.

pronounced vasoconstriction in both feet, especially in the affected extremity. In case 5, in which there was only a 5 per cent increase in flow, the disease was in a late stage of atrophy and all readings were low.

The average increase in blood flow in the 12 cases was slightly above 30 per cent in the affected extremity. This remarkable increase persisting over many months and years is the most characteristic feature of the syndrome. Its possible mechanism will be discussed in subsequent paragraphs. Of interest was the behavior of such extremities when they were subjected to changes in environmental temperature. While the room temperature was kept at 28 C. (82.4 F.), the temperature of the water bath varied from 15 C. (59 F.) to 40 C. (104 F.). Figure 2 shows that at lower temperatures the difference between the two sides was not as great as at higher temperatures. The affected extremity did not respond with vasoconstriction in a cooler bath as readily as did the normal limb. One would expect such reactions in the presence of a chronic vasodilatation. Occasionally, however, there is a masked vasoconstriction in such limbs, which may account for some paradoxic responses.

BLOOD FLOW AFTER SYMPATHECTOMY

A total of 23 determinations of blood flow prior to and 18 following sympathectomy were made on 4 patients. In spite of the already increased blood flow on the affected side, there was a further increase following operation in 3 of 4 cases. The interpretation of these findings, together with observed clinical relief, will be given in the discussion.

STUDIES ON CALCIUM METABOLISM

Determinations of blood calcium, phosphorus and phosphatase were made for 12 patients affected with reflex dystrophy. In 4 cases the determinations were repeated several weeks apart. While the values for calcium and phosphorus were normal, the phosphatase was slightly but definitely elevated in most instances

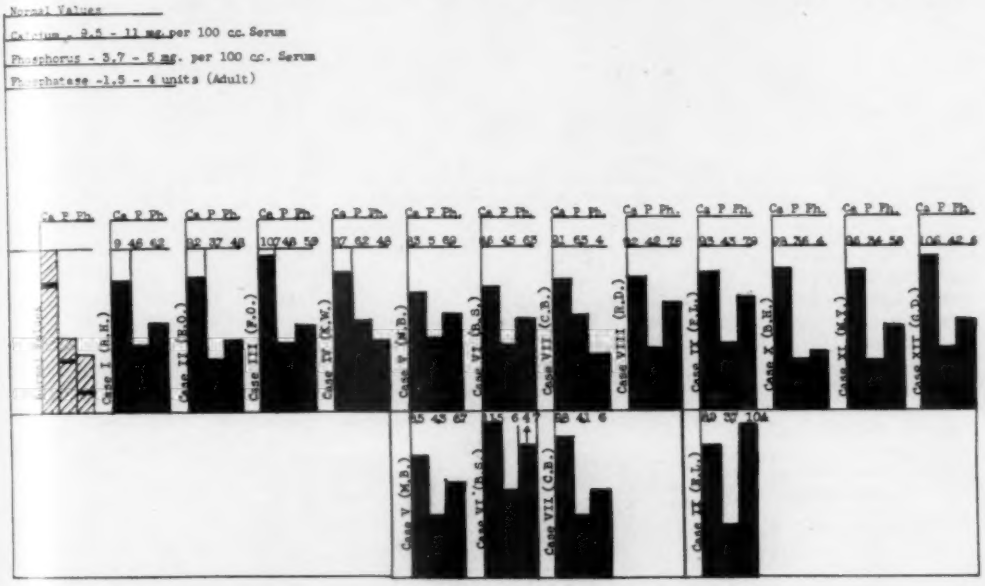


Fig. 3.—Studies of calcium, phosphorus and phosphatase in Sudeck's atrophy.

(fig. 3). The upper level of normal expressed in Bodansky units is 4. This figure was obtained in case 10 (B. H.), in which a spotty atrophy of the carpal bones developed after a blunt injury of the dorsum of the hand. Obviously only a small area of bony structure was involved. The highest reading, on the other hand, of 10.4 units, was obtained in case 9, in which the patient had a diffuse osteoporosis of the entire upper extremity following a fracture of the shoulder. This woman was 58 years old, and her traumatic osteoporosis may well have merged with a senile osteoporosis.

We have insufficient data on other forms of atrophy of bone, but it is possible that the phosphatase level may give an indication of the extent of osseous atrophy and especially of the presence of reconstructive activity.

THE COURSE OF THE DISEASE

There are mild types of reflex dystrophy which subside spontaneously in a few weeks or rapidly respond to local or paravertebral infiltrations of procaine hydrochloride. There are types of moderate severity causing continuous pain, increasing contractures of tendons and joints and extreme decalcification of bone.

The patients are completely disabled. The course is self limited, however, and there may be spontaneous healing within a year, residual stiffness, deformity and contractures being left in spite of an insignificant original injury. There is, finally, a severe form which causes a spreading neuralgia, a spreading osteoporosis and a gradual mental fixation on the intractable lesion. The patients may request amputation or threaten or commit suicide. A functional and economic rehabilitation is hardly ever obtained. The patients may require permanent institutional care (figs. 4 and 5).

The severity of the original injury does not determine the course of the disease. Severe trauma causing fracture of long bones and total transection of nerves and blood vessels does not seem to be followed by this syndrome. Sprains, contusions, mild frostbites or burns, partial injuries to nerves and venous thromboses are in the history of patients with Sudeck's atrophy (table 2). One has the impression after studying these patients that their autonomic nervous system is

TABLE 2.—*Sudeck's Atrophy: Character of Trauma and Duration of Symptoms Prior to Treatment*

Initial Trauma	Number of Cases	Duration of Symptoms in Months
Sprined ankle	8	8, 2, 4, 4, 3, 12, 42, 8
Sprained ankle and fractured fibula	2	5, 24
Dislocated ankle	1	7
Infection at inner ankle	1	5
Sprained wrist	2	1, 3
Wringer injury to wrist	2	7, 36
Colles' fracture	1	12
Crushed finger	4	12, 6, 6, 48
Blunt injury to dorsum of hand	2	1, 1
Fracture of navicular bone	1	18
Blunt injury to dorsum of foot	1	5
Injury to shoulder	2	9, 78
Periphlebitis	4	36, 36, 8, 20
Blunt injury to lower leg	1	14
Scar following incision of toe	1	6
Total number of cases	33	

unstable. One cannot help referring to animal experiments which indicate that when cortical release is produced by decortication an autonomic reflex, such as gastric contraction after stretching, is exaggerated.[8] There are also clinical observations to show that a hemiplegic extremity shows overactivity of the sympathetic nervous system.[9] It would seem, then, that certain emotional states, such as anxiety and fear, as well as uncontrolled pain, are capable of facilitating vascular reflexes which normally subside in a few days.

THE NATURE OF THE REFLEX

In figure 6 we have summarized our concept of vascular reflexes arising from traumatic stimuli in the extremities. Trauma in the broad sense of the word may consist of a mechanical, chemical or thermal injury or a vascular occlusion. Somatic sensory fibers carry impulses centrally from such an area. In *A* the nerve impulse never reaches the cord but produces an efferent vasodilatation, an axon reflex. In *B* vasodilatation has been activated through a spinal cord reflex. This pathway is

8. Hesser, F. H.; Langworthy, O. R., and Kolb, L. C.: Experimental Study of Gastric Activity Released from Cortical Control, J. Neurophysiol. **4**:274, 1941.

9. Pilcher, C.; Wyatt, T. E., and Carney, H. M.: Infarction of the Brain with Unilateral Circulatory Changes, Arch. Neurol. & Psychiat. **45**:321 (Feb.) 1941.

Fig. 4.—Minnie B., a 46 year old woman, twisted her ankle. She immediately complained of severe, continuous pain. At an emergency station a fracture of the fibula was diagnosed. A posterior molded splint was applied. Two weeks later another cast was applied. After the second cast had been worn for five weeks, adhesive strapping was used. She still had continuous pain and could not bear weight on the foot. Because of the disproportion between the pain and the solidly healed fracture, malingering was suspected. A general anesthetic was given, and during the first stage moderate pressure, which elicited a painful response, was applied to the injured ankle.. At the time she was first seen by one of us (D. S. M.) the foot was in a pronounced equinus position, the skin was glossy and cyanotic and the ankle was swollen. There was an increased growth of hair on this area, and the nails were ribbed. The patient refused all therapy and at the time of writing remains incapacitated.

Fig. 5.—Roentgenograms of Minnie B. taken two years after she suffered a sprained ankle with a fracture of the fibula. The bones of the left foot show a diffuse osteoporosis and a "ground glass" appearance. Roentgenograms of both hips and of the spine showed a moderate osteoporosis. The osteoporosis was first visible two months after the injury and was first a spotty type of atrophy, which gradually became diffuse.

postulated by Toennies,[10] but its existence is denied by Dole and Morison.[11] In *C* the efferent sympathetic vasoconstrictors have been activated, but vasodilatation is also possible through the sympathetic outflow.

It seems to us that, as was shown by Albert [12] in 1924 for the dog, all trauma results in vasomotor reactions which, unlike the much emphasized reflex vasoconstrictions, are predominantly vasodilator. Applied to the present problem of Sudeck's atrophy, the vasodilator reflexes first predominate, but may give way later to vasconstriction.

In figure 7 we illustrate the axon reflex more in detail. Its persistence and gradual spread is consistent with the clinical picture of Sudeck's atrophy. In this diagram the stimulus *b* is shown to spread centripetally to the next division, from which it travels centrifugally, but it also travels in a centrifugal direction from the point of stimulation. This type of spread would explain the observation of Tinel,[13] confirmed by Sir Thomas Lewis,[14] that blocking or sectioning of a peripheral nerve distal to the source of irritation may bring relief.

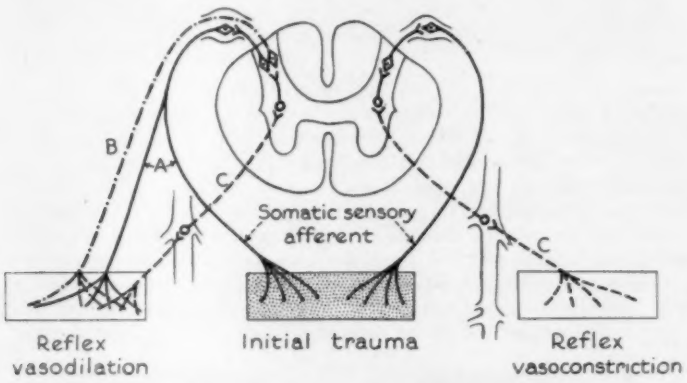


Fig. 6.—Vasomotor reflexes of the extremities.

THE VALUE OF SUCH A WORKING HYPOTHESIS

The diagrams shown have a definite value in outlining treatment. If the syndrome is recognized within the first few weeks, when osteoporosis is not even present, the repeated block of the local area, together with satisfactory immobilization, may abort the disease. It is a curious fact that men like Böhler,[15] who strictly immobilize most injuries but encourage early weight bearing and active motion, either have not seen the syndrome under discussion or have not deemed it worthy of mention. The early control of continuous nerve stimulation seems,

10. Toennies, J. F.: Reflex Discharge from the Spinal Cord over Dorsal Roots, J. Neurophysiol. **1**:378, 1938.

11. Dole, V. P., and Morison, R. S.: A Note on the Question of Reflex Activation of Dorsal Root Dilators, Am. J. Physiol. **130**:304, 1940.

12. Albert, F.: Étude expérimentale des troubles vaso-moteurs réflexes d'origine traumatique, Arch. internat. de physiol. **22**:391, 1924.

13. Tinel, J.: Le système nerveux végétatif, Paris, Masson & Cie, 1937.

14. Lewis, T.: Experiments Relating to Cutaneous Hyperalgesia and the Spread Through Somatic Nerves, Clin. Sc. **2**:373, 1936.

15. Böhler, L.: Treatment of Fractures, translated by M. E. Steinberg, Vienna, Wilhelm Maudrich, 1929.

then, of importance. It is more difficult to explain the value of repeated sympathetic blocks, although clinically there can be no doubt about their efficacy in early stages. The same difficulty is encountered in explaining the benefit of sympathectomy for patients with the more advanced conditions. There are three possible explanations which need to be examined.

First, it is possible that the painful stimuli which give rise to vasodilatation travel centripetally in the sympathetic fibers. It is true that a sympathetic block promptly abolishes the causalgia or burning pain of this syndrome, but it does not abolish the vasodilatation. The pain, then, is not due to vasodilatation, at least not to the kind that results from blocking the vasoconstrictors. It would seem that afferent sympathetic fibers, whose existence in the periphery is denied by the great majority of investigators, are not involved.

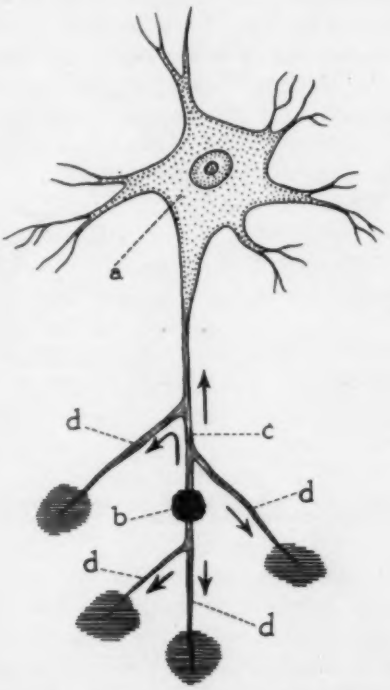


Fig. 7.—The axon reflex shown in figure 6 is reemphasized in this diagram. The stimulation of the nerves results in the production of pain-producing substances. Unless somatic sensory nerves are capable of antidromic conduction, such phenomena postulate the existence of posterior root efferent fibers, a theory which is supported by the persuasive evidence of Toennies.[10]

The second possibility is that the vasodilatation in Sudeck's atrophy is transmitted by efferent vasodilators in the sympathetic nervous system. There is no doubt about their existence in man.[16] However, if this mechanism were operative one would expect a decrease of blood flow after sympathectomy, whereas the increase in blood flow persists in spite of the relief from pain.

The third possibility is that the vasodilator efferent fibers of the posterior root system, which are stimulated directly or reflexly by the injury, secrete a pain substance which is diffusible and which would explain the peculiar type of hyper-

16. Lewis, T., and Pickering, G. W.: Vasodilation in the Limbs in Response to Warming the Body, with Evidence of Sympathetic Vasodilator Nerves in Man, Heart **16**:33, 1931.

esthesia encountered in Sudeck's atrophy. These fibers correspond to the "nocifensor system" of Sir Thomas Lewis.[14] Sympathectomy, then, would not interfere with any nervous pathway but might "wash out" or eliminate the pain substance.[17] Similarly herpes zoster, which is due to an irritation of the posterior root system, can be rendered painless and made to heal after paravertebral block.[18]

We have no conclusive evidence for the last explanation but have used it as a working hypothesis. It may be that sympathectomy, as Hyndman and Wolkin [19] recently stated, results in capillary constriction and thus eliminates some of the vasodilatation, but this would hardly explain the relief of pain that this operation affords.

TREATMENT

For the disease in the early, mild stage, sufficient immobilization and repeated infiltrations of procaine hydrochloride into the injured area seem almost specific. When the neuralgia has spread beyond the site of injury, the glove or stocking type of hyperalgesia may be successfully treated by paravertebral injections of procaine hydrochloride. As Homans [20] pointed out, these injections may give relief for a longer and longer period until the pain is entirely abolished. When sympathetic block abolishes the symptoms but they recur with undiminished intensity after a few hours or days, sympathetic ganglionectomy is not to be postponed. There is, finally, a group of cases of a severe, intractable form of the disease associated with compensation neurosis, drug addiction and mental imbalance which may be caused in part by continuous suffering, for which treatment is of no avail.

TABLE 3.—*Results of Treatment in Sudeck's Atrophy*

Type of Treatment	Number of Cases	Recovery *		
		Complete	Partial	None
Cast, splint, physical therapy	8	1	3	4
Repeated procaine block	1	..	1	..
Repeated sympathetic block	5	4	1	..
Periarterial sympathectomy	3	2	1	..
Perivenous stripping	2	2	..	..
Sympathetic ganglionectomy	8	5	3	..
No treatment	6	..	2	4
Total	33	14	11	8

* Complete recovery, restoration of function; partial recovery, cessation of pain with limitation of function; no recovery, stationary or deteriorating physical or mental status.

Table 3 summarizes the various forms of treatment employed. Since some of the patients were seen late, after contractures, ankylosis and severe osteoporosis had developed, the efficacy of treatment cannot be judged without considering the stage of the disease at the same time. Generally speaking, conservative treatment may lead to a slow, spontaneous regression of the disease with cessation of pain and recalcification of bone; however, the changes in the joints and the shortening of the tendons allow only a partial recovery. Repeated block with procaine hydrochloride was employed in only 1 case, in which today we should prefer sympathetic block. Periarterial sympathectomy resulted in complete recovery in 2 cases and partial

17. Gask, G. E., and Ross, J. P.: The Surgery of the Sympathetic Nervous System, ed. 2, Baltimore, William Wood & Company, 1937.

18. de Takáts, G., and Miller, D.: Unpublshed data.

19. Hyndman, O. R., and Wolkin, J.: The Autonomic Mechanism of Heat Conservation and Desiccation: I. Effects of Heating the Body, Am. Heart J. **22**:289, 1941.

20. Homans, J.: Minor Causalgia Following Injuries and Wounds, Ann. Surg. **113**:932, 1941.

recovery in 1 case, but with increasing experience we would prefer repeated sympathetic blocks for these patients. Perivenous stripping in 2 patients suffering from reflex dystrophies following venous occlusion has been successful. Sympathetic ganglionectomy gave excellent results in 5 and fair results in 3 patients. In the latter group, 1 operation was incomplete; in the other 2 cases changes in the joints and tendons were so far advanced that orthopedic correction became necessary.

Of the 8 patients who obtained no relief, 4 were treated conservatively and 4 refused any type of treatment. Two of this group are in closed institutions, 2 could not be traced and 4 have litigations pending.

CONCLUSIONS AND SUMMARY

It is our impression, on the basis of clinical observations, studies on blood flow and results of treatment, that the syndrome of Sudeck's atrophy is the result of a chronic stimulation of somatic and possibly of efferent vasodilator fibers; the reflex may soon subside, or it may become chronic and progressively increasing in its effects. Pain, localized and spreading, vasodilatation and osteoporosis characterize the fully developed syndrome, but osteoporosis is a comparatively late manifestation. In fact, reflex dystrophy is most amenable to treatment in the early weeks and months; it becomes more intractable and requires more and more radical intervention if early treatment is not instituted. The trauma which it follows is usually a blunt injury near a joint or a nerve trunk, such as the interosseous, the saphenous or the posterior tibial nerve. The part is often inadequately immobilized. The emotional status of the patient may well exaggerate these phenomena, as cortical release often does in case of autonomic reflexes.

The treatment must fit the duration and severity of the syndrome and consists of repeated injections of procaine hydrochloride into the injured area, paravertebral sympathetic block, periarterial sympathectomy and sympathetic ganglionectomy. Orthopedic correction may be needed in the cases of advanced atrophy after the pain has subsided.

SOLITARY BENIGN ENCHONDROMA OF BONE

HENRY L. JAFFE, M.D.
AND
LOUIS LICHTENSTEIN, M.D.
NEW YORK

By solitary benign enchondroma of bone we mean the benign cartilaginous growth which begins its development in the interior of an affected bone and involves only a single bone in any 1 subject. Our records include 28 instances [1] of this type of lesion, and the discussion which follows is based largely on these. To judge from our experience, the lesion appears mainly in phalanges (particularly those of the hand), in metacarpal bones and in the humerus and femur, though other bones of the limbs are occasionally the site. Although our own cases do not include any in which the lesion was in a bone other than one of a limb, it should be noted that instances of such localization have also been reported.

A benign enchondroma may be present in the interior of a bone without causing any obvious distention. However, it is not unusual to find, especially if the lesion is in a short tubular bone (phalanx or metacarpal or metatarsal bone), that some part of the affected area is distended in consequence of thinning and bulging of the overlying cortex. Still, the mere fact that the central cartilaginous growth has strongly bulged out the overlying cortex for some distance should not lead, as it often does, to clinical misinterpretation of such an enchondroma (central chondroma) as an osteochondroma (osteocartilaginous exostosis).

For a long time it has been known that a benign enchondroma may undergo malignant transformation into a chondrosarcoma. This is by no means a rare occurrence in connection with an enchondroma in a long tubular bone. Indeed, in a number of cases of central chondrosarcoma of such a bone which we have studied [1a] we have been able to trace the evolution out of an originally benign central chondromatous lesion. The transition is usually slow, and indeed years may elapse before one is finally faced with an obvious chondrosarcoma.

Most of the contemporary papers dealing with solitary benign enchondroma present accounts of single cases or at most 2 or 3 and stress the clinical details and often particularly the relevant surgical procedures rather than the pathologic changes. From some of the reports it is impossible to tell whether a particular case actually represents an enchondroma (central chondroma) or an osteochondroma (osteocartilaginous exostosis). Often an article does not even contain a statement as to whether a given enchondroma (or, more vaguely, chondroma) discussed was a solitary lesion or was associated with similar lesions in other skeletal parts. That is, cases of solitary enchondroma are sometimes not distinguished from cases of dyschondroplasia (skeletal enchondromatosis; Ollier's disease). Finally, one is sometimes unable to decide on the basis of the information reported in a paper whether a given lesion is still a benign enchondroma or, as one suspects from the general picture, has become a chondrosarcoma.

From the Laboratory Division, Hospital for Joint Diseases.

1. Since the time of writing, we have studied 2 additional cases. In 1 case, the lesion was in the terminal phalanx of the third finger of a woman of 37. In the other, it was in the fifth metacarpal bone of a girl of 19.

1a. Lichtenstein, L., and Jaffe, H. L.: Chondrosarcoma of Bone, Am. J. Path., to be published.

It is our intention in this paper (1) to sketch the clinical and roentgenographic findings in cases of solitary benign enchondroma; (2) to consider the pathologic (and especially the cytologic) structure of the lesion; (3) to indicate the cytologic changes which appear if the lesion is undergoing transformation into a chondrosarcoma, and (4) to point out the bearing of these various considerations on the management of pertinent cases.

CLINICAL ASPECTS

Sex and Age Incidence.—Of the patients in our series of 28 cases, 12 were males and 16 females; that is, there seems to be no significant sex difference in incidence. In respect to age of the patients at the time of admission to the hospital for treatment, only 1 was under 10 and only 1 over 50 years of age while 16 were between 11 and 30 and 10 between 30 and 50. As to age at onset of the complaints, it appears that the history was sometimes one of only a few weeks or months but sometimes one of many years, irrespective of the age on admission. It should be pointed out, however, that in connection with involvement of a humerus or femur (as compared with the involvement of other bones) the interval between the onset of clinical manifestations and the time of admission was consistently short. Except in 1 instance, in which it was one and one-half years, it uniformly amounted to only some weeks or months. Possibly this is explicable through the greater disability involved and the consequently greater attention given when clinical manifestations start to appear in relation to long bones.

Localization.—Apparently, as already noted, solitary benign enchondroma has a predilection for limb bones. As to the site of the lesion in our 28 cases, this was a finger phalanx in 13, a metacarpal bone in 5, a humerus in 5, a femur in 3, a toe phalanx in 1 and a metatarsal bone in 1. Indeed, the lesion is found in bones of the hand in particular, and our findings in this respect are in harmony with those of Mason.[2] Evidently, to judge from our material, which seems fairly representative, localization of the lesion in a toe phalanx or a metatarsal bone is not as common as certain blanket statements in the literature would lead one to believe. If these blanket statements are checked against actual case reports, it appears that relatively few of these reports relate to lesions in toe phalanges or metatarsal bones. As to localization in long tubular bones, however, our findings are in accord with those reported in the literature in suggesting that among these the humerus and femur are the most likely to be affected. In regard to involvement of ribs, pelvic bones, vertebrae or skull bones, which is by no means common, it is often difficult to be certain of the point of origin and the real nature of the lesion, as is pointed out by Menne and Frank,[3] for instance, in respect to certain chondromas in bones of the skull.

Benign enchondromas of short or long tubular bones begin their development in the metaphysis as a rule, although by no means always (see footnote 4). A central chondroma beginning within a metaphysis may eventually involve a large portion of the shaft and even extend into the corresponding epiphysial end of the affected bone. It by no means necessarily grows into the adjacent epiphysis, however, and apparently does not do so in any case until the epiphysis has fused with the shaft; that is, it does not tend to violate the epiphysial cartilage plate.

According to the prevailing view, benign enchondromas of bone arise from misplaced cartilage rests. In relation to lesions developing in the metaphysis of tubular bones, the source of these rests is generally stated to be cartilage snared

2. Mason, M. L.: Tumors of the Hand, Surg., Gynec. & Obst. **64**:129 (Feb.) 1937.

3. Menne, F. R., and Frank, W. W.: So-Called Primary Chondroma of the Ethmoid, Arch. Otolaryng. **26**:170 (Aug.) 1937.

off from an epiphysial cartilage plate. The principal basis for this conception has been that at autopsy in cases of healing rickets foci of cartilage apparently derived from the cartilage plates have been found in the metaphyses of tubular bones.

Possibly even in persons who have not had rickets, cartilage apparently derived from the cartilage plates may be found persisting in the metaphyses, even into old age. Indeed, Scherer,[3a] from Schmorl's laboratory, stated that lentil-sized to cherry-pit-sized cartilage rests were found in the right femur in 20 of 1,125 cases (1.7 per cent) in which this bone was routinely removed and examined. The subjects were all over 25 years of age. The rests were found in the metaphyses of the femur, at most a few centimeters from an epiphysial cartilage plate, with a heavy predilection for the upper metaphysis. The rests usually showed considerable evidence of regressive change, the cartilage having undergone a good deal of calcification and cystification in some cases and even heavy ossification in others. Undoubtedly, many cartilage rests, after undergoing involution, may eventually completely disappear. However, Scherer cited the case of a woman of 58 in whom, as an incidental finding at autopsy, an enchondroma measuring 8.5 cm. in length was noted in the upper metaphysis of the right femur. This lesion was believed to have evolved out of a rest such as those just mentioned which subsequently underwent a spurt of growth instead of regressing completely or at least remaining static. This case was presented by Scherer as evidence in favor of the view that solitary benign enchondroma may originate from a cartilage rest snared off from an epiphysial cartilage plate.

Clinical History.—A common history in the cases of phalangeal involvement was that the patient was not aware of anything wrong until a local trauma was followed by pain and swelling and a roentgenogram revealed an altered phalanx with a pathologic fracture. On the other hand, some patients gave a history of a spontaneous, not particularly painful or only intermittently painful swelling of the region of the affected phalanx, dating back perhaps several years but recently exacerbated by a local trauma. The general mildness of the clinical complaints is further attested by the fact that the condition often ran through several episodes of local trauma and disability, indicating repeated fractures through the affected phalanx. On examination, one can usually palpate at least a limited enlargement of this phalanx. The enlarged region is likely to be rather firm, and if there has been a recent fracture through the area there may be considerable local tenderness and even some heat.

The history patterns in the cases of involvement of metacarpal and metatarsal bones were essentially the same as in those of phalangeal involvement. The patients usually also presented a local swelling of the affected bone, and when there was pain (apparently from a fracture) after trauma the pain subsequently subsided though the swelling persisted.

In the cases in which long bones were affected, the clinical complaints, as already noted, were usually of rather recent date. Nevertheless, it seems probable that in these cases the lesion had been present for a long time, often for years, though latent, before the onset of manifestations. Thus, for instance, in 1 patient, a physician, the lesion was discovered by chance seventeen years before it began to cause any trouble, and then the difficulty, of two and one-half months' standing, ensued when a pyogenic infection became superimposed on the enchondroma in a femur. Another patient, a woman who showed in a femur a heavily calcified

3a. Scherer, E.: Exostosen, Enchondrome und ihre Beziehung zum Periost, Frankfurt. Ztschr. f. Path. **36**:587, 1928.

enchondroma which must have been in existence for many years, presented herself only because of local pain of six months' duration aggravated by walking and possibly attributable to a new spurt of growth of the lesion. Still another patient, a young girl who presented an extensive lesion in a humerus, was admitted because of pain, tenderness and disability attributable to a pathologic fracture ten days previously, but she stated that a year before there had been a fracture through the same area, which had healed promptly.[4]

ROENTGENOGRAPHIC FINDINGS

Phalanges.—In phalanges (fig. 1 *A, B, C, D* and *E*), the lesion appears as a more or less oval rarefaction shadow. This may be situated centrally within the affected bone and may even fail to cause distention of the neighboring cortex. On the other hand, it may be situated off to one side (eccentrically) and may even cause a pronounced bulging distention and thinning of the overlying cortex. Those enchondromas which are situated eccentrically usually show a delicate radiopaque line where they abut on the uninvolved portion of the phalanx. The rarefaction shadow as a whole usually looks more or less cloudy and may present a vaguely trabeculated appearance and even densifications ranging in size from that of a pinhead to that of the head of a match. These densifications reflect foci of ossification in the cartilage and constitute telltale indications of an enchondroma. Frequently, one can note evidence of a still unhealed fracture. As also shown by these roentgenograms, as long as the epiphysis has not fused with the shaft, the former is not involved, and even after fusion the epiphysis is not necessarily invaded.

Solitary benign enchondroma is by far the most common and indeed the principal solitary lesion affecting phalanges. In fact, any lesion situated in a middle or proximal phalanx of a finger and presenting anything like the roentgenographic picture described and illustrated is almost certainly a benign enchondroma. Nevertheless, a benign enchondroma is not infrequently misdiagnosed roentgenographically as a cyst, a giant cell tumor or an osteochondroma. As already pointed out elsewhere,[5] solitary bone cyst of the type commonly occurring in long tubular bones rarely (if ever) occurs in phalanges, and indeed we ourselves have never seen it in the latter. As to giant cell tumor, in the strictly limited sense in which we understand this lesion,[6] we have never observed it in a phalanx, though we must allow for the bare possibility of its occurrence in such a bone. At any rate, in tubular bones it seems never to start its development elsewhere than in the epiphysial end of the bone, in contrast to enchondroma, which practically always starts its development in the metaphysial shaft region of such a bone. An enchondroma which has conspicuously distended part of the cortex may be misinterpreted as an osteochondroma if attention is concentrated on the bulge to the neglect of the appearance of the interior of the bone.

---

4. We have not included in this paper a case of solitary benign enchondroma in which the lesion began its development in an epiphysis and was confined to the latter. It seems expedient to give it at least brief mention. The lower epiphysis of a femur was the site of the lesion, and the patient was a child of 1½ years at the time of admission to the hospital. It is interesting that during the subsequent four years, before the lesion was resected and while it was enlarging until it occupied practically the entire condyle, it did not break through the plate and extend into the shaft. The lesion was originally treated by irradiation, without benefit, and indeed the growth even continued to enlarge under this treatment, although the irradiation was conducted strictly along accepted lines.

5. Jaffe, H. L., and Lichtenstein, L.: Solitary Unicameral Bone Cyst, Arch. Surg. **44**:1004 (June) 1942.

6. Jaffe, H. L.; Lichtenstein, L., and Portis, R. B.: Giant Cell Tumor of Bone, Arch. Path. **30**:993 (Nov.) 1940.

The only two solitary lesions which occur in phalanges (though rarely) and which may also simulate enchondroma roentgenographically are squamous epithelium–lined cyst and ossifying fibroma. Epithelium–lined phalangeal cyst [7] seems to occur exclusively in terminal phalanges of fingers and indeed nearly always in the terminal half of such a phalanx, a site which is rare for benign enchondroma. When occurring in digits, ossifying fibroma (osteogenic fibroma), so far as our experience is concerned, is likewise located in terminal phalanges, but of toes, not of fingers, a location again extremely rare for a solitary enchondroma.

Metacarpal and Metatarsal Bones.—In regard to metacarpal and metatarsal bones (fig. 1 *F, G* and *H*), the roentgenographic findings are essentially similar to those in regard to phalanges. It is to be noted, however, that in metacarpal

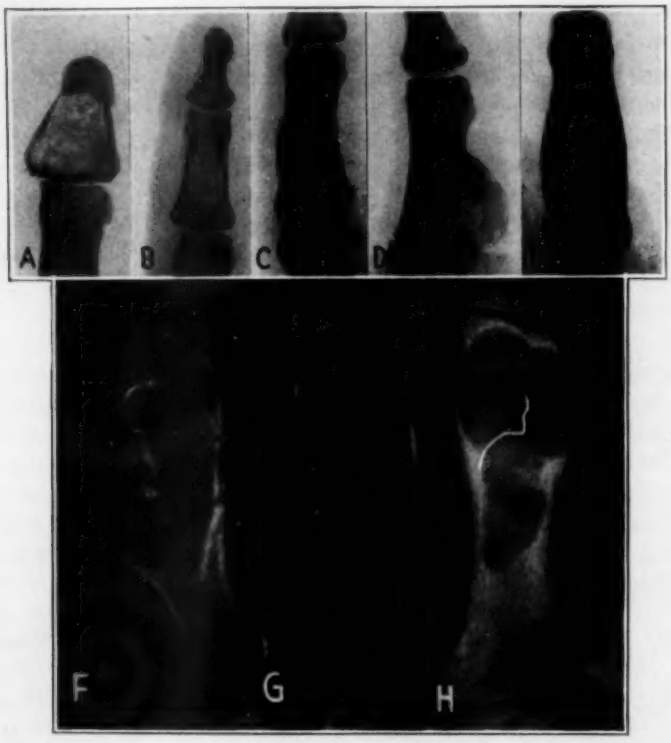


Fig. 1.—*A, B, C, D* and *E*, roentgenograms from 5 different cases, illustrating various roentgen aspects of solitary benign enchondroma in phalanges, as discussed in the text. The nature of all these lesions was verified by examination of the tissue. *F, G* and *H*, roentgenograms from 3 different cases, illustrating various aspects of solitary benign enchondroma in metacarpal bones, as discussed in the text. The nature of all these lesions was verified by examination of the tissue.

or metatarsal bones the enchondroma tends to be more or less in the distal instead of the proximal part of the shaft, though it is thus still oriented toward the epiphysis of the bone. The remarks on the differential diagnosis so far as they pertain to solitary unicameral cyst, giant cell tumor and osteochondroma apply as closely to metacarpal or metatarsal as to phalangeal enchondroma. Epithelium-lined inclusion cyst apparently does not occur in a metacarpal or metatarsal bone.

7 Bissel, A. D., and Brunschwig, A.: Squamous Epithelial Bone Cysts of the Terminal Phalanx and Benign Subungual Squamous Epithelial Tumor of Finger, J. A. M. A. **108**:1702 (May 15) 1937.

Ossifying fibroma (osteogenic fibroma) or a solitary focus of fibrous dysplasia,[8] however, apparently occasionally does occur in a metacarpal or metatarsal bone. Roentgenographically, such a lesion in a metacarpal bone could simulate an enchondroma quite closely. Merely on the basis of probability, however, the likelihood is greater that one would be dealing with enchondroma, the latter being the

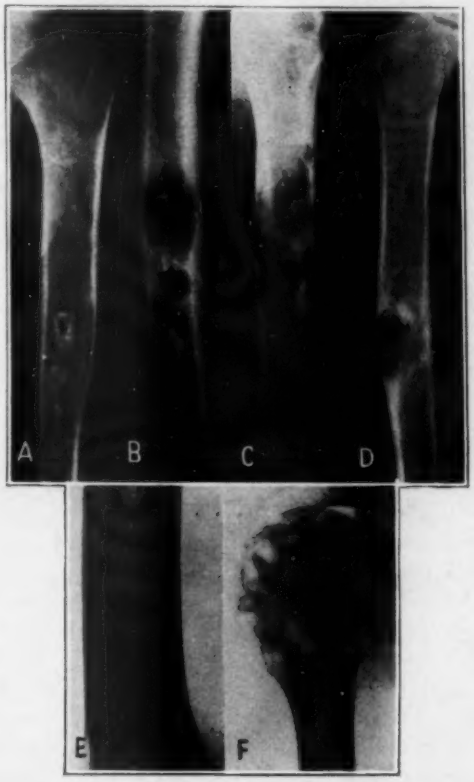


Fig. 2.—Roentgenograms illustrating various appearances presented by solitary benign enchondroma in long bones and verified by examination of the tissue. In *A*, the presence of radiopaque spots and blotches in the metaphysis and the rest of the shaft is already strong evidence in favor of the diagnosis of enchondroma. In *B*, the same is also true, and the patient (a physician) knew of the presence of this lesion for seventeen years. (Figure 4 *B* shows calcifying cartilage from one of the radiopaque areas.) In *C*, the roentgenographic picture is ambiguous. Specifically, the roentgenogram is more strongly suggestive of fibrous dysplasia than of enchondroma. In *D*, too, the diagnosis would be difficult to make on the basis of the roentgenogram alone. (Figure 3 *B* represents cartilage tissue taken from the area of rarefaction.) *E* shows the roentgenogram of a strictly central calcifying and ossifying enchondroma in the lower part of the shaft of a femur. (Figure 3 *A* represents tissue from this lesion). *F* shows a highly calcified and ossified enchondroma involving the upper end of the shaft and the head of the humerus. At the time this roentgenogram was taken, the lesion was already beginning to undergo transition into a chondrosarcoma. (Figure 5 represents tissue obtained from this lesion on two occasions ten months apart.)

---

8. Lichtenstein, L., and Jaffe, H. L.: Fibrous Dysplasia of Bone: A Condition Affecting One, Several, or Many Bones, the Graver Cases of Which May Present Abnormal Pigmentation of Skin, Premature Sexual Development, Hyperthyroidism, or Still Other Extraskeletal Abnormalities, Arch. Path. **33**:777 (June) 1942.

more common lesion in the bones in question. Should the lesion present stippled foci of densification, one would have strong evidence of its actually being an enchondroma.

Long Bones.—In regard to long bones (fig. 2), much of what has been said about the roentgen findings in enchondroma of a phalanx or a metacarpal bone is still applicable. A considerable part of the shaft may be involved, and the lesion is likely to be more strictly central. If the cortex does bulge, it is probable that the bulge will be slight and limited to a relatively small area. The presence of spotty or blotchy calcification points rather definitely in the direction of an enchondroma. Indeed, even a few scattered pinhead-sized to match-head-sized spots of densification would point in that direction. On the other hand, when the presence of radiopaque spots is doubtful or when they are absent entirely, the diagnosis of enchondroma cannot be made with any confidence. Especially if the lesion (of course solitary) also appears somewhat expanded and trabeculated, the strongest likelihood is that it represents a solitary focus of fibrous dysplasia, and another, though weaker, possibility is that it represents a solitary unicameral bone cyst rather than an enchondroma.

PATHOLOGIC ASPECTS

One does not often have the opportunity of examining a solitary enchondroma intact in its setting, for ordinarily the gross material available from a lesion consists merely of fragments of cortex from the site of surgical entry and curettings from the interior of the affected area of bone. The material consisted of these in all but 2 of the 28 cases discussed here. In these 2[9] cases intact lesions were examined, 1 in a surgically extirpated metacarpal bone and the other in a surgically resected lower end of a femur.

The extirpated metacarpal bone showed general bulging of the contour of its shaft anteriorly, exaggerated on the distal half by two distinct hemispherical bulges, a smaller and a larger one. Sectioning of the bone in both the longitudinal and transverse axes revealed that the marrow cavity of the shaft was substantially filled by cartilage tumor tissue, which in general was bluish white and faceted. Where the contour of the bone was distended, it could be seen that tumor cartilage was bulging forward under an attenuated cortex. In the region of the two humps, the cortex had been reduced to paper thinness.

The specimen from the lower end of the femur showed when sawed sagittally an eccentrically situated tumor mass of the size of a large walnut. The tumor hugged the cortex on one side but did not distend it and was so located also that about half of its mass was situated in the lower end of the diaphysis and half extended into the epiphysial end of the bone. The tumor was so highly calcified and ossified that it appeared, on the whole, yellowish and gritty, though islands of tissue clearly recognizable as cartilage were still in evidence.

On the basis of the material from the other cases, it can be said in general that the fragments of cortical bone will be found thin and even shell-like if they come from an affected area where the cortex has been bulged out, as is commonly the case when the lesion is in a phalanx or a metacarpal or metatarsal bone. On the other hand, the cortical fragments may show but little thinning or none if they come from a lesion which has failed to bulge the cortex, a state of affairs not uncommon when a long tubular bone is affected. The medullary surface of the cortical fragments, whether they are only slightly or greatly thinned, usually shows some erosive ridging and grooving. The periosteal surface is

9. These 2 specimens are from the collection of pathologic material preserved by the late Viennese pathologist Jacob Erdheim and now housed in the laboratory of this hospital.

ordinarily found smooth and without evidence of apposition of new bone unless the cortical fragments have come from a site of recent infraction.

The tissue obtained by curettement from the interior of the lesion consists in some cases almost entirely of faceted bits of bluish white, firm or even somewhat myxomatous hyaline cartilage. However, such lesions may also yield some

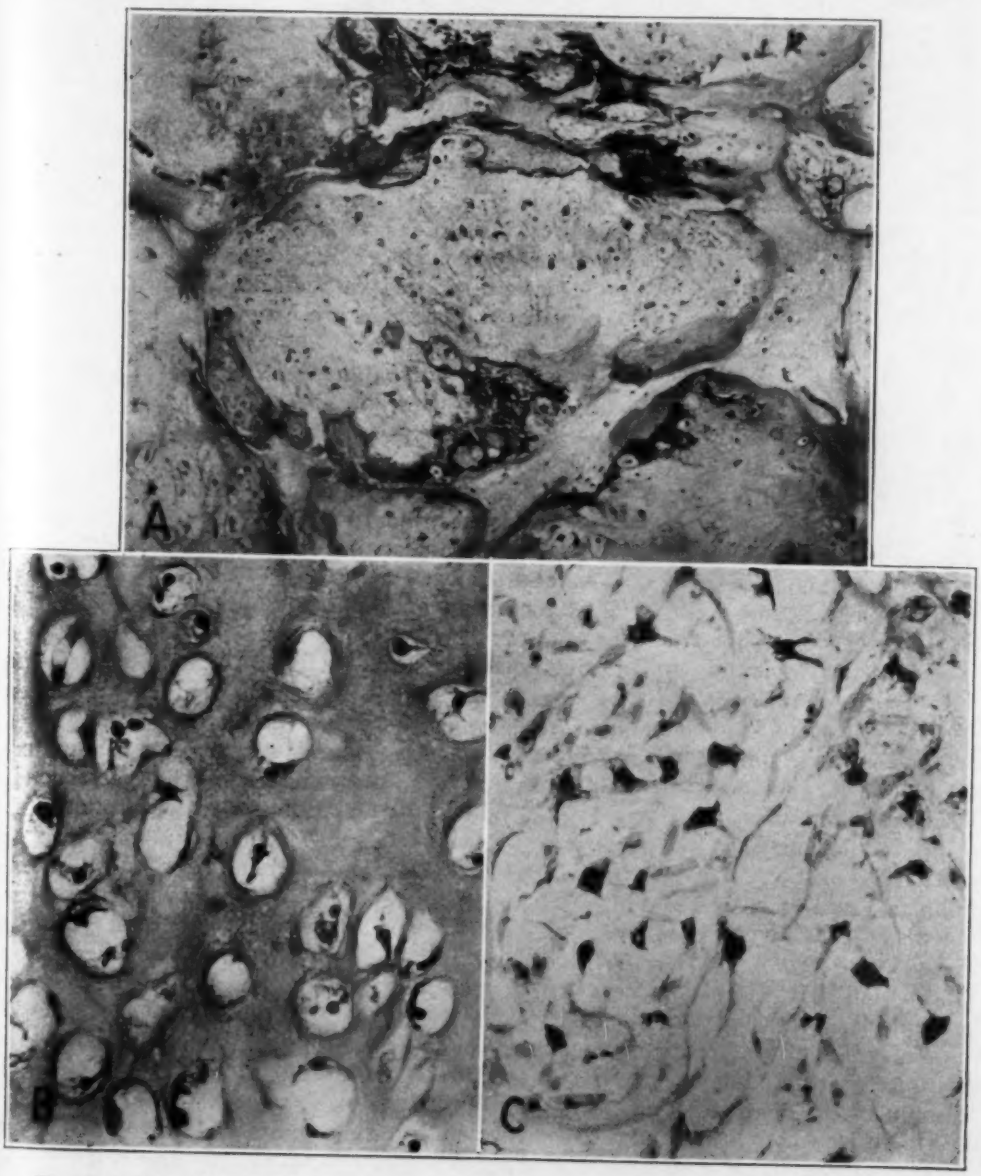


Fig. 3.—Photomicrograph (× 80) showing the architecture of the lobules of cartilage, which in this section are undergoing calcification and ossification, especially about the periphery. (This tissue represents some of the less heavily calcified cartilage curetted from the lesion illustrated in figure 2 *E*.) *B*, photomicrograph (× 240) showing hyaline cartilage the cells of which are surrounded by lacunas. *C*, photomicrograph (× 240) showing cartilage whose intercellular material is edematous and mucoid and whose cells no longer lie in clearcut lacunas. Note that in both *A* and *B* there seem to be no binuclear cells and the cell nuclei are relatively small (compare with figure 4 *C* and *D*, which are from chondrosarcomas).

bits of dull white cartilage and yellowish, definitely gritty tissue representing heavily calcified and even ossified cartilage. On the other hand, the curettings from still other lesions may consist mainly of obviously calcified and ossified cartilage and may be only meagerly interspersed with islands of hyaline cartilage.

Calcification, and also ossification, of a chondroma is best interpreted as a process of regression or aging or even of healing. In our cases it was more pronounced, on the whole, in the lesions involving long bones, especially of adults. It was also moderately pronounced in some of the lesions in phalangeal and metacarpal bones, especially of the middle-aged adults. Apparently it can be induced artificially by intense irradiation of the lesion.

Microscopically, too, the tendency of the cartilage tissue to be divided off into fields or lobules (fig. 3*A*) is of course apparent, though more so in some specimens and in some areas than in others. Frequently the facets of cartilage are separated by clefts, and it is not difficult to deduce from comparison of different fields the course of evolution of these spaces. They are formed at sites of swelling and fusion of cartilage cell lacunas associated with disintegration of the cells within. Eventually many of the spaces thus created are invaded by blood vessels. If the cartilage immediately bordering on the spaces becomes calcified or ossified, the space may even come to contain some fatty and myeloid marrow. Furthermore, the individual benign enchondromas vary in respect to cellularity. Some are rather rich in cells; others are relatively poor, and still others show intermingled richly and poorly cellular areas.

In part or throughout, the intercellular ground substance may be hyaline. When it is, the cells, as a rule, lie in lacunas, many of which may be fairly large, and a lacuna does not usually contain more than one cell, though some lacunas show two and an occasional one may show even a nest of cells (fig. 3*B*). In some areas the intercellular substance may appear edematous or even mucoid, and where it does the cartilage cells tend no longer to be surrounded by lacunas and their cytoplasm is found multipolar or stellate (fig. 3*C*). Apparently an early stage of this regressive process is represented by unmasking of the collagen fibers and an acidophilic-staining tendency of the ground substance.

In sections stained with hematoxylin, such ground substance as is undergoing calcification will at least look dusty, in consequence of the presence of calcareous granules in it (fig. 4*A*). When the calcification is more pronounced, the granules may be particularly conspicuous around lacunas and also at the periphery of the cartilage lobules, especially where the latter border on interlobular vascular spaces. Where the calcareous status is clearly pronounced, the cartilage cells may be found to have undergone necrobiosis or even to have disappeared completely (fig. 4*B*). Heavily calcified areas, especially where they border on the vascular spaces, may even undergo ossification by process of metaplasia.

In attempting to evaluate the benignity of a cartilage tumor, one should concentrate on the cellular elements and specifically on those in the viable and not too heavily calcified areas. Also, one should avoid tissue from the immediate sites of fractures. In representative areas the cartilage cells of a clearly benign enchondroma will be found consistently small. Their cytoplasm is pale and often more or less vacuolated, and its outlines are frequently indistinct. Their nuclei, too, are consistently small and are roundish and dark staining. Indeed, practically all of the cartilage cells of a benign enchondroma present essentially this appearance, whether or not they lie in lacunas and irrespective of the size of the latter if they do. Scanning many preserved fields from as many parts of the lesion as possible, one may find cartilage cells which, though small, contain two nuclei. However, some lesions show practically no cells of this kind, while in others most of the

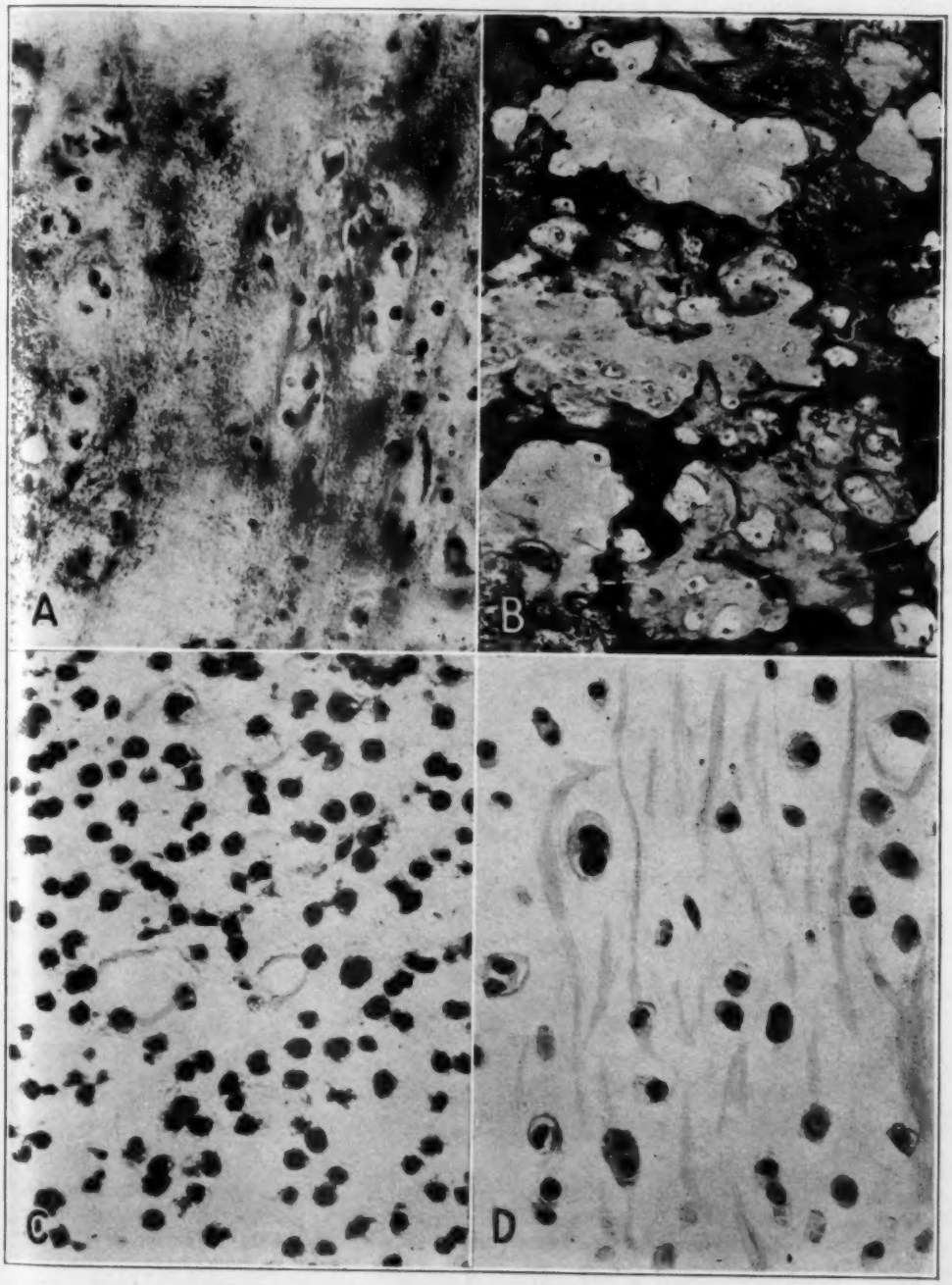


Fig. 4.—*A*, photomicrograph (× 240) showing heavy calcareous dusting of the intercellular material of the cartilage. *B*, photomicrograph (× 76) showing an area of heavily calcified cartilage. *C*, photomicrograph (× 240) from a chondrosarcoma the cytologic structure of which is not yet crudely and obviously sarcomatous. *D*, photomicrograph (× 250) from another chondrosarcoma of the same kind. However, note that in both *C* and *D* the nuclei are plump, and many of the cells have plump double nuclei. Compare these illustrations with those of benign cartilage growths shown in figures 3 *B* and *C* and 4 *A*.

fields will show none, but an occasional field will show one or two or even several. Such binuclear cartilage cells are cells in process of amitotic division, and a clearly benign enchondroma does not show cartilage cells in mitosis.

Altogether, then, solitary benign enchondromas of bone vary in respect to degree of cellularity, distribution of the cells, presence or absence of lacunas about the cells and amount and character of the ground substance between the

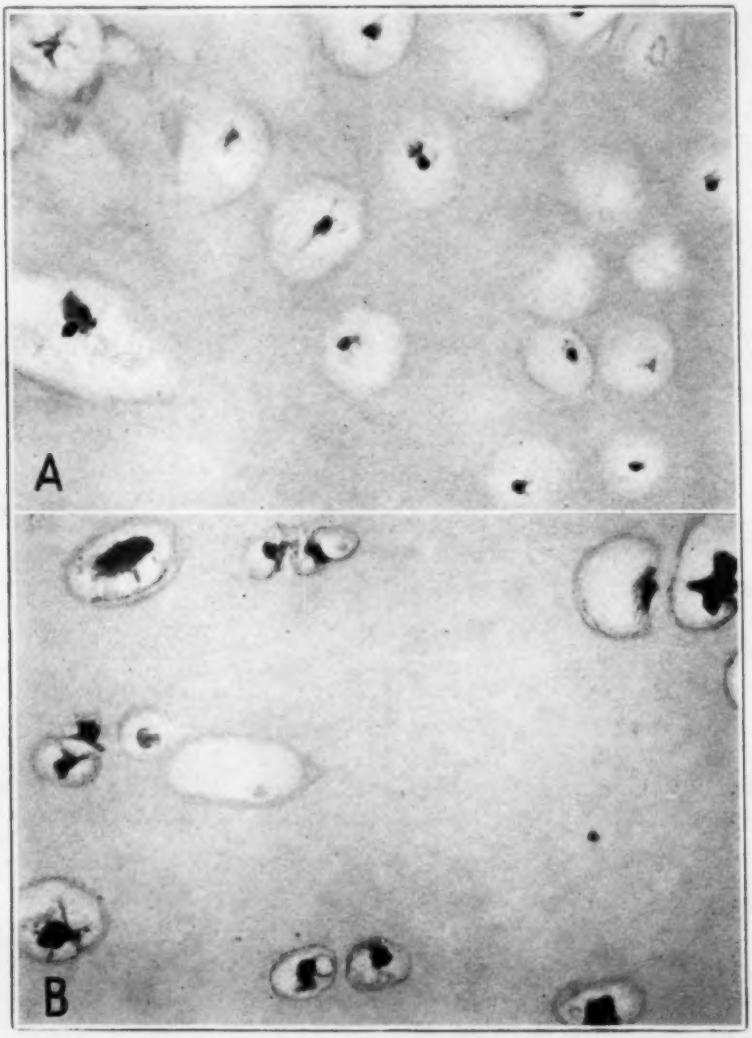


Fig. 5.—*A*, photomicrograph (× 240) of biopsy material obtained from the lesion shown in figure 2 *F*. Note that there is only one cell containing two nuclei and furthermore that these nuclei, as well as all the other nuclei shown, are small. Compare this with the photomicrographs of other benign enchondromas (figs. 3 *B* and *C* and 4 *A*) shown under the same magnification. *B*, photomicrograph (× 240) showing a field from the same case as that represented by *A*, but taken ten months later and specifically from the presection specimen. Fields like it were found only here and there among the sections. Note the change in the character of the cells, in particular the presence now of cells with giant nuclei and multiple nuclei and the plumping of the nuclei even in the uninuclear cells.

cells. What stamps the lesion as benign cytologically is the fact that the viable cartilage cells are rather small and their single nuclei definitely not plump.

While one does find, here and there, some cells (still small) with two nuclei, one does not find them regularly in all fields, even in small numbers. (See, for instance, figures 3 *B*, 3 *C* and 4 *A*, and compare with figures 4 *C* and 4 *D*, all of which represent the same magnification.)

As already noted, benign enchondroma (especially in a long tubular bone) sometimes undergoes malignant transformation. As a benign growth, the lesion may have been present for many years and may even have been entirely symptomless until there was a change in its nature. Prior to its revivescence and malignant transformation, the enchondroma may even have become extensively calcified and ossified. The evolution of a chondrosarcoma out of a benign enchondroma, though sometimes rapid, is usually an extremely slow process. Early in this evolution, cytologic evidence of change in the direction of malignity is already present.[1a] However, at this stage, as we have shown more fully elsewhere,[1] the significant cytologic aberrations are by no means obvious and furthermore are usually present only in scattered fields. To recognize them, one has to take due cognizance of the characteristic cytologic pattern of the benign lesion as described and watch for such deviations from that pattern as the presence of more than an occasional binuclear cell and a general plumping-up of the nuclei. If one finds, even if only in scattered areas, many microscopic fields showing several or more binuclear cartilage cells, or many cartilage cells with plump nuclei, and especially any cartilage cells containing large or multiple nuclei, the growth is no longer a clearly benign enchondroma. It may not be until much later, however, that the histologic picture of the lesion is that of a crudely obvious chondrosarcoma.

In a pertinent case [10] in which the upper end of a humerus was involved, the initial surgical intervention was removal of tissue for biopsy, which seemed to confirm the clinical diagnosis of a calcifying and ossifying enchondroma (fig. 2 *F*). However, after the removal of tissue the patient experienced increasing pain in the affected area and increased loss of function, and it was evident from comparative roentgen examinations that the lesion was growing, slowly but steadily. For these reasons, ten months after the operation the upper end of the humerus was resected and the defect filled in by insertion of a substantial portion of the upper end of a fibula. Reexamination and comparison of the biopsy and resection specimens (figs. 5 *A* and 5 *B* respectively) leave no doubt that one was dealing with a chondrosarcoma in the early stages of its evolvement out of a benign enchondroma. However, the patient has shown no recurrence during the subsequent four and one-half years.

TREATMENT AND PROGNOSIS

In general, the treatment of choice for solitary benign enchondroma of bone is surgical. It consists specifically of curettement, perhaps followed by chemical cauterization and, in addition, under appropriate circumstances, collapse of the distended part of the cortical wall and introduction of bone chips or insertion of a solid bone graft. Of the 14 phalangeal lesions, some were merely curetted, some were curetted and cauterized and some were curetted and filled with bone chips, sometimes after and sometimes without cauterization. No recurrences were noted in any of these cases, and healing was prompt and uncomplicated in all of them except 1. In that case, a course of preoperative irradiation therapy had been given. The precise dosage which was used is not known to us, but the

10. Burack, P. I.: Ossifying Enchondroma of Head of Humerus, Bull. Hosp. Joint Dis. **1**:3 (March) 1940.

patient stated that she had received "10 x-ray treatments of the lesion, without benefit." After the operation, the wound suppurated slightly and a number of the bone chips which had been inserted were sequestrated. One cannot, of course, be sure that this complication was ascribable to the preoperative irradiation, but that, in general, heavily irradiated lesions in bone subsequently operated on are particularly susceptible to infection is well known.

Of the 6 lesions in metacarpal and metatarsal bones, 5 were likewise treated by curettement, collapse of the cortical wall and introduction of bone chips or a solid graft. In these cases, too, the postoperative course seems to have been uniformly favorable and apparently there were no recurrences. The exception noted was the case in which the entire metacarpal bone was extirpated, apparently because of the extensiveness of involvement of this bone. No follow-up is available in this case, but anatomically the lesion was clearly an entirely benign one.

The same principles of treatment were followed in regard to 5 of the 8 lesions of long tubular bones, again with uniformly good end results. Of the other 3, 1 (a femoral lesion) was treated (elsewhere) by resection of the lower end of the affected bone. Such treatment is obviously too radical for a solitary benign enchondroma, though the surgeon may have felt that by being drastic he was forestalling malignant transformation of the lesion. As to the other 2, removal of tissue for biopsy constituted the original surgical intervention in 1 of them,[11] while in the other (as previously noted) a biopsy was followed ten months later by resection of the affected upper end of the humerus, since in the interval the lesion showed clinical progression in the direction of malignancy.

SUMMARY AND CONCLUSIONS

The clinical (including therapeutic), roentgenographic and pathologic aspects of solitary benign enchondroma of bone have been described on the basis of 28 cases from our files. As its name implies, the lesion is a benign cartilaginous growth which develops in the interior of an affected bone and involves only a single bone in any 1 subject. The lesion has a definite predilection for bones of the limbs, particularly the phalanges of the fingers, the metacarpal bones, the humerus and the femur.

In relation to tubular bones, the lesion starts its development within the shaft and apparently within a metaphysial region in particular. It may come to involve a considerable portion of the shaft. On the other hand, it may extend into the adjacent or nearer epiphysis, though it is not likely to do this until after the epiphysis has fused with the shaft. In the course of its development, the lesion may remain strictly confined within the interior of the bone without bulging out the cortex anywhere. More often, however, it thins and distends the cortex, creating a bulge which can be detected even clinically.

Apparently the lesion is not more common in one sex than in the other. Though the great majority of the patients are adolescents or young or middle-aged adults when presenting themselves for treatment, the lesion seems usually to be already of long standing at that time. The clinical complaints are generally mild. Usually swelling has been noted in the affected part, and there may be

11. In this case, the lesion, in the upper end of the humerus of a man of 52 years, appeared to be a heavily calcified and ossified enchondroma. The biopsy tissue already revealed microscopically some scattered groups of cartilage cells with plump nuclei, so that when we restudied the slides in connection with the writing of this paper we were aware that this enchondroma possessed aggressive qualities. Several weeks after this manuscript was submitted for publication, the patient returned with a frank chondrosarcoma. There had been an interval of twelve months between the diagnostic biopsy and the resection of the upper end of the humerus on account of the obvious chondrosarcoma which had developed in the meantime.

some pain and tenderness as well, especially when trauma has induced infraction of the distended cortex.

The roentgenogram is a valuable guide in the diagnosis of solitary benign enchondroma. In relation to enchondromas in long tubular bones, the presence of radiopaque dots or even blotches representing foci of calcification and ossification often enables one to make the correct diagnosis even when the roentgenographic appearance of the lesion is otherwise ambiguous. In relation to phalanges and metacarpal and metatarsal bones, the chances are strong that one is dealing with an enchondroma if a fairly large area of rarefaction associated with thinning and bulging of the cortex is seen. This is true even in the absence of spotty calcification, just on the basis of the relative commonness of the lesion in these bones.

The ultimate decision as to whether a central cartilaginous growth in bone is benign must be based on the cytologic findings. The picture of benignity is created by the character of the cells (as observed in viable and not too heavily calcified areas of the lesion) and specifically by the following features: (1) The vast majority of the cartilage cells have only one nucleus; (2) this nucleus tends strongly to be rather small and definitely not plump in relation to the cell as a whole; (3) such cells as are binuclear are still small, still have small (and not plump) nuclei and are found only occasionally and even then only in scattered fields.

An enchondroma, especially of a long tubular bone, may undergo malignant transformation. Cytologically, in the early stages of this transition the lesion will deviate from the benign pattern just sketched, at least in showing in scattered fields many cells with plump nuclei, more than an occasional cell with two such nuclei and even some giant cartilage cells with large single or multiple nuclei.

In connection with the management of solitary benign enchondroma, good end results are to be expected from conservative surgical intervention.

1919 Madison Avenue.

PRIMARY CARCINOMA OF THE INFRA-AMPULLARY PORTION OF THE DUODENUM

WITH EXAMPLE OF PROBABLE ORIGIN FROM ABERRANT PANCREATIC TISSUE

G. LYMAN DUFF, M.D., PH.D.
AND
H. L. FOSTER, M.D.
MONTREAL, CANADA
AND
WILLIAM W. BRYAN, M.D.*
LONDON, ONTARIO, CANADA

Primary carcinoma of the duodenum is usually classified according to its relation to the ampulla of Vater as supra-ampullary, periampullary and infra-ampullary. In any of these situations, carcinoma of the duodenum is rare. In a series of 350,286 autopsies, Eger [1] found an incidence of 0.033 per cent. According to Hoffman and Pack,[2] carcinoma of the duodenum constituted 0.3 per cent of all intestinal carcinomas, while Eger [1] stated that 45.6 per cent of carcinomas of the small intestine are found in the duodenum. Of these, 24.9 per cent were supra-ampullary, 61.9 per cent were periampullary and 13.1 per cent were infra-ampullary.[2] If carcinomas arising from the ampulla and papilla of Vater, which should be classified as tumors arising from the biliary tract, are excluded, the percentage of tumors arising in the periampullary portion approximates that of growths arising in the supra-ampullary portion.[3]

In 1937 Lieber, Stewart and Lund [4] in a critical review of the literature found 62 cases of carcinoma of the infra-ampullary portion of the duodenum. However, they were able to accept as authentic only 28 cases, since in the remainder insufficient data had been given to establish the diagnosis. They described 2 new instances of carcinoma of the infra-ampullary portion of the duodenum. Since that time there have been reported 5 additional cases,[5] in only 3 of which was there a postmortem examination.[6]

The clinical features and the gross and microscopic appearance of carcinoma of the duodenum have been fully described in other papers [7] and will be referred

From the Department of Pathology, McGill University.
* Formerely of the Department of Radiology, Royal Victoria Hospital, Montreal, Carleton B. Pierce, M.D., Radiologist-in-Chief.

1. Eger, S. A.: Primary Malignant Disease of Duodenum, Arch. Surg. **27**:1087 (Dec.) 1933.

2. Hoffman, W. J., and Pack, G. T.: Cancer of Duodenum, Arch. Surg. **35**:11 (July) 1937.

3. Harbin, W. P.; Harbin, W. P., Jr., and Harbin, L.: Ann. Surg. **101**:961, 1935.

4. Lieber, M. M.; Stewart, H. L., and Lund, H.: Carcinoma of Infrapapillary Portion of Duodenum, Arch. Surg. **35**:268 (Aug.) 1937.

5. (*a*) Bergendal, A.: Acta radiol. **20**:417, 1939. (*b*) Claiborn, L. N., and Dobbs, W. G. H.: Surgery **4**:97, 1938. (*c*) Macindoe, P. H.: M. J. Australia **1**:48 1940. (*d*) Pollock, S.: Radiology **31**:362, 1938.

6. Bergendal.[5a] Claiborn and Dobbs.[5b] Macindoe.[5c]

7. (*a*) Eusterman, G. B.; Berkman, D. M., and Swan, T. S.: Ann. Surg. **82**:153, 1925. (*b*) Mateer, J. G., and Hartman, F. W.: Primary Carcinoma of Duodenum, J. A. M. A. **99**:1853 (Nov. 26) 1932. (*c*) Meyer, J., and Rosenberg, D. H.: Primary Carcinoma of Duodenum, Arch. Int. Med. **47**:917 (June) 1931. (*d*) Eger.[1] (*e*) Hoffman and Pack.[2] (*f*) Lieber, Stewart and Lund.[4]

to only briefly. The patient complains of epigastric distress, usually aggravated by food and relieved by vomiting. Nausea is usually associated with the vomiting, and as the condition progresses the vomiting becomes more frequent. In the cases of infra-ampullary carcinoma, the vomitus contains bile. In addition to these symptoms, there is anorexia with loss of weight going on to cachexia. Patients often complain of attacks of diarrhea alternating with attacks of constipation. Examination of the stools may show the presence of occult blood. A mass in the epigastrium may be noted. The duration of the illness from the onset of symptoms is from three to eighteen months, with an average of seven months. Of 30 patients with carcinoma of the infra-ampullary portion of the duodenum whose cases were reviewed by Lieber, Stewart and Lund [4] 20 were men ranging in age from 40 to 74 years and averaging 58 years, while 10 were women with an age range of 35 to 61 years and an average age of 48 years.

In relatively few of the published cases of primary carcinoma of the duodenum has the condition been diagnosed roentgenologically. In contrast to the pathologic descriptions, the roentgen findings regarding the duodenum have been variously reported as normal, or as due to pyloric obstruction. On the occasions when a definite localization of the lesion has been accomplished, the defect usually has been ascribed to extrinsic pressure or to an invasive process from some extrinsic lesion. Rarely has an intrinsic lesion of the duodenum been considered.

Carman [8] believed that cancer of the supra-ampullary area could not be differentiated roentgenologically from ulcer. The serrated appearance of the second and third portions of the duodenum normally produced in the barium pattern by the valvulae conniventes and the commonly rapid motility in that area make the diagnosis of early cancer in these areas difficult in the absence of obstruction. Shanks [9] stated: "In these cases there is a considerable tendency to obstructive ileus. . . . Radiographically a duodenal ileus is evident and possibly a filling defect from the obstructing growth." In a recent paper, Bergendal [5a] commented that the difficulty in recording and correctly diagnosing primary duodenal cancer is due to the position of the duodenum and its close proximity to adjacent organs.

Roentgenologic examinations were performed in 18 of the 30 cases collected by Lieber, Stewart and Lund.[4] In only 6 of the 18 was the lesion correctly located.[10] The several roentgenologists had considered that the lesions were due to adhesions, pressure defects from an intrinsic tumor or pressure defects from mesenteric vessels. In some instances, no opinion was recorded. It was only on the third examination in Bergendal's first case that a roentgenologic diagnosis of primary duodenal cancer was given. Hellmer [11] thought that the demonstrated intraluminal defect in Bergendal's second case might be due to either a primary carcinoma of the duodenum or an invasion of the duodenum by a carcinoma of the pancreas.

Pathologically, carcinoma of the duodenum may be either of the scirrhous, annular type composed of firm, dense white tissue or of the soft, polypoid, pedunculated, medullary type. Ulceration is common. Stenosis with complete or almost complete occlusion of the lumen of the bowel, dilatation of the stomach and the proximal portion of the duodenum and compensatory hypertrophy of the walls

8. Carman, R. D.: The Roentgen Diagnosis of Diseases of the Alimentary Tract, ed. 2, Philadelphia, W. B. Saunders Company, 1920.

9. Shanks, S. C.; Kerley, P., and Twining, E. W.: A Text-Book of X-Ray Diagnosis, London, H. K. Lewis & Co., Ltd., 1938, vol. 2.

10. Fariñas Mayo, L.: Bol. Liga contra el cáncer **9**:210, 1934. Lundberg, S.: Acta chir. Scandinav. **56**:417, 1924. Kellogg, E. L.: The Duodenum, New York, Paul B. Hoeber, Inc., 1933. Pauchet, V., and Luquet: Bull. Acad. de méd., Paris **97**:276, 1927. Sala, A. M.: Radiology **25**:437, 1935. Mateer and Hartman.[7b]

11. Hellmer, cited by Bergendal.[5a]

are among the most striking gross features. The tumors infiltrate the adjacent retroperitoneal tissue and the contiguous parts of the pancreas. The common sites of metastases are the regional lymph nodes and the liver, while occasionally the lungs, bones and peritoneum are involved. However, metastases are said to occur late in the course of the disease. Among the 30 cases collected by Lieber, Stewart and Lund [4] ulceration of the tumor was present in 16, the growth was completely annular in 19 and obstruction was complete or almost complete in 17. The scirrhous type of tumor was the commonest. Metastases occurred in 50 per cent of the cases.

Histologically, the tumors are of a cylindric cell type; in some instances the cells are well differentiated and in others extremely anaplastic. They may be columnar or cuboidal, with the usual neoplastic characteristics, and occur in solid nests or in acinar formation. The annular tumors have abundant stroma with few cells, while

Fig. 1.—Roentgenogram showing marked dilatation of the duodenum proximal to an area of narrowing (indicated by arrow) which involves the third part of the duodenum. The gastric outline is normal.

the medullary lesions have scant stroma with abundant cells. The tumors in which ulceration has occurred show inflammatory changes.

The following case of primary carcinoma of the infra-ampullary portion of the duodenum is reported because of the rarity of the condition, because it demonstrates the possibility of reaching a correct clinical diagnosis by means of careful roentgenologic examination and because it illustrates the possibility of origin of carcinoma of the duodenum from aberrant pancreatic tissue.

REPORT OF A CASE

W. J., a 35 year old Polish man, was admitted to the Royal Victoria Hospital with the following history:

He was a restaurant worker, a heavy smoker and drinker. He was in his usual good health until six months before admission to the hospital, when he began to have attacks of epigastric pain coming on late after meals and relieved by food. These symptoms progressed. One month before admission, he began to complain of constipation and failing appetite with loss of weight and strength. One week before admission he started to vomit with increasing

frequency, up to five or six times daily, and even after taking fluids. He then consulted a physician for the first time and was admitted to the hospital.

The physical examination revealed a thin man showing evidence of recent loss of weight. The abdomen was diffusely tender, but no abdominal mass was palpable. There was a non-tender, firm, nodular mass palpable in the anterior wall of the rectum and fixed to the surrounding tissues. Small subcutaneous nodules were present over the whole body but were most numerous on the left thigh and the right side of the neck. The gastric juice contained no free hydrochloric acid, and the total acidity was from 20 to 40. The hemogram showed 5,400,000 red blood cells, 7,900 white blood cells and a hemoglobin content of 100 per cent.

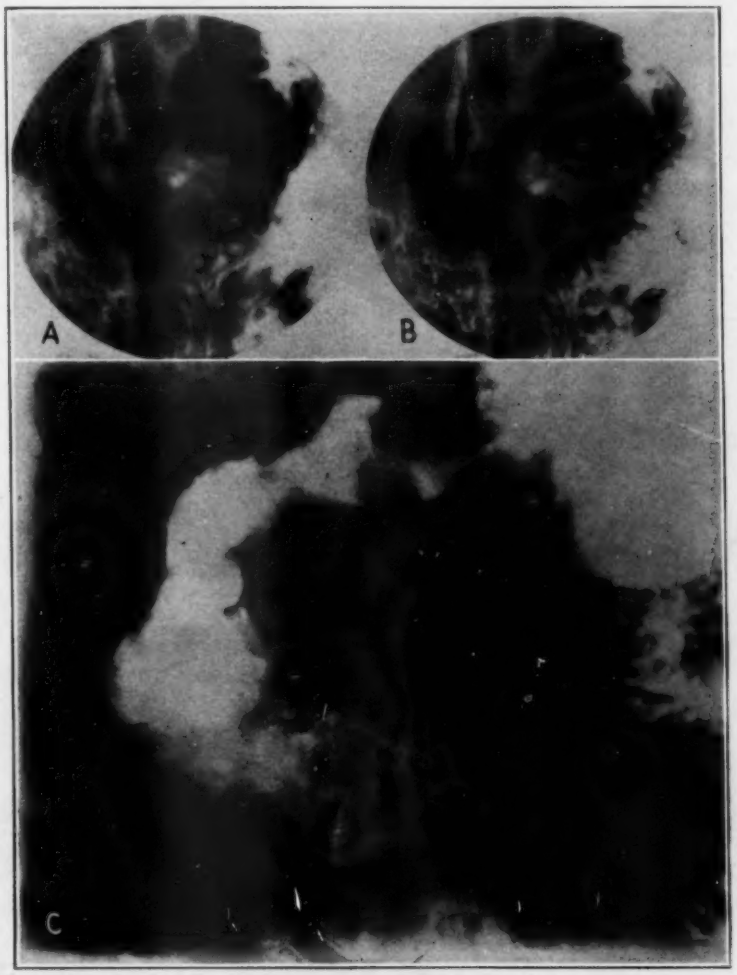


Fig. 2.—*A* and *B*, serial roentgenograms taken with local compression. The ulcer crater is shown overlying the left superior margin of the body of the third lumbar vertebra. *C*, roentgenogram showing concentric narrowing of the duodenal lumen distal to the ulcer and dilatation of the second portion of the duodenum proximal to the ulcer.

The fragility of the red blood cells was normal and the sedimentation velocity and the prothrombin time were slightly prolonged. There was no hyperbilirubinemia.

On roentgen examination (figs. 1 and 2) there was found just distal to the junction of the second and third portions of the duodenal loop a definite narrowing with irregularity of the lumen of the duodenum. Only a small channel just proximal to the duodenojejunal junction permitted barium to pass to the jejunum with the persistence of a fleck of barium having the appearance of opaque material retained in an ulceration. Extreme tenderness to palpation was present over this region. Four hours later 60 per cent of the barium meal

remained in the stomach. The opinion of the roentgenologist was: "The zone of deformity and irregularity and narrowing, involving the distal portion of the duodenal loop, is due to an intrinsic lesion of the duodenum, probably neoplasm, with an ulcerated area in this zone."

Eleven days after the patient's admission to the hospital an exploratory laparotomy was done by Dr. J. C. Armour, who found a large tumor mass involving the duodenum at the duodenojejunal junction. There were numerous metastases to the parietal peritoneum and along the mesenteric attachment of the small intestine. A biopsy of a nodule in the omentum showed adenocarcinoma. The vomiting persisted, and the patient's condition became progressively worse. He died four weeks after operation, or about seven and a half months after the onset of symptoms.

Postmortem Examination.—A complete autopsy was performed four hours after the patient's death. In the following summary only the observations pertaining to the duodenal tumor will be described.

Fig. 3.—Photomicrograph showing microscopic appearance of the margin of the duodenal ulcer. Note the abrupt termination of duodenal mucosa which is essentially normal in structure and has no connection with the mass of tumor tissue in the submucosa.

In the duodenum, a firm nodular mass measuring 6 by 4 cm. was found almost completely encircling the infra-ampullary portion, infiltrating the adjacent fatty tissue and displacing the pancreas superiorly. Examination of the lumen of the duodenum revealed a deep ulcerated area with a soft necrotic base and overhanging edges about 1.5 cm. distal to the ampulla of Vater, in the superior aspect of the duodenum. Just distal to this, the tumor mass bulged into the lumen but the covering mucosa was intact, though hemorrhagic. The bulging mass produced almost complete obstruction of the duodenum for a distance of 2.5 cm. The cut surface of the tumor was firm and was mottled yellow and gray with small hemorrhagic areas. The duodenal wall was thickened by tumor tissue which appeared to have spread beneath the mucosa. The uncinate process and adjacent parts of the head of the pancreas were displaced rather than invaded by the tumor, as indicated by a distinct line of demarcation between tumor and pancreatic tissue. The stomach and the proximal portion of the duodenum were markedly distended and the walls thickened by hypertrophy of the muscle coats. Along the mesenteric border of the small intestine were small, firm, white metastatic tumor nodules.

These in some areas involved the muscular coat, but the mucosa was everywhere intact. The peritoneal surfaces of the rectovesical pouch, the right lumbar gutter, the inferior aspect of the right side of the dome of the diaphragm and the greater omentum were studded with tumor nodules.

Microscopic Examination.—Histologic sections of the duodenal wall including the area of ulceration showed a large mass of tumor tissue which lay chiefly in the submucosa. The

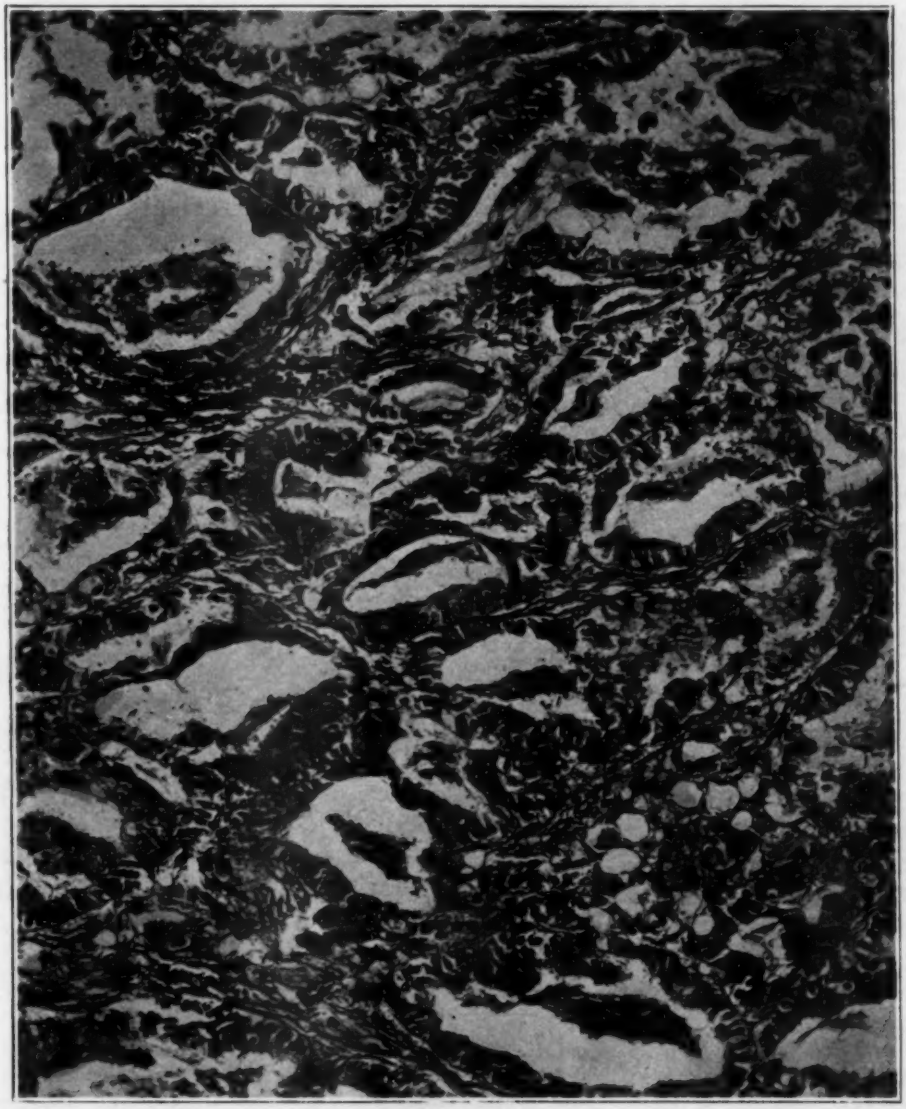


Fig. 4.—Photomicrograph showing the histologic structure of the tumor. The formation of ductlike spaces lined by cuboidal or columnar epithelium is a prominent feature. Several papillary ingrowths of the lining cells are shown. In most areas the stroma was much more abundant than in this field.

submucosal layer of tumor was deepest in the region just distal to the ulcer, but a thinner layer of neoplastic tissue was present in the base of the ulcer and spread through the submucosa for a considerable distance in all directions. The duodenal mucosa was elevated by the tumor, but it was not at any point connected with the tumor tissue and apart from some hemorrhagic extravasations it was relatively normal in appearance. At the margins of the

ulcer the mucosa was interrupted abruptly and showed no neoplastic or hyperplastic changes and no continuity with the underlying tumor cells (fig. 3). The tumor tissue, apart from a few small solid clusters and strands of tumor cells, was composed of many ductlike structures of varying size and shape, lined by cuboidal or columnar epithelial cells which in some areas were thrown up into irregular papillary folds. Their cytoplasm was acidophilic; the nuclei varied greatly in size, shape and depth of staining. Mitotic figures were present in small numbers. The fibrous stroma was moderate in amount. Altogether, the histologic structure was similar to that of a pancreatic carcinoma of duct cell type (fig. 4). The tumor had extended between the muscle bundles and beyond the muscle coats of the duodenum into the peripancreatic fat. The mass of tumor tissue came into immediate contact with the pancreas but was sharply demarcated from it throughout much the greater part of the area of contact. A slight degree of invasion of individual pancreatic lobules was demonstrable in only a few microscopic areas (fig. 5). In the mass of tumor tissue which lay nearest the pancreas careful search failed to reveal any evidence that pancreatic tissue had been replaced by tumor. The tumor mass in this region contained no remnants of normal pancreatic ducts, acini or

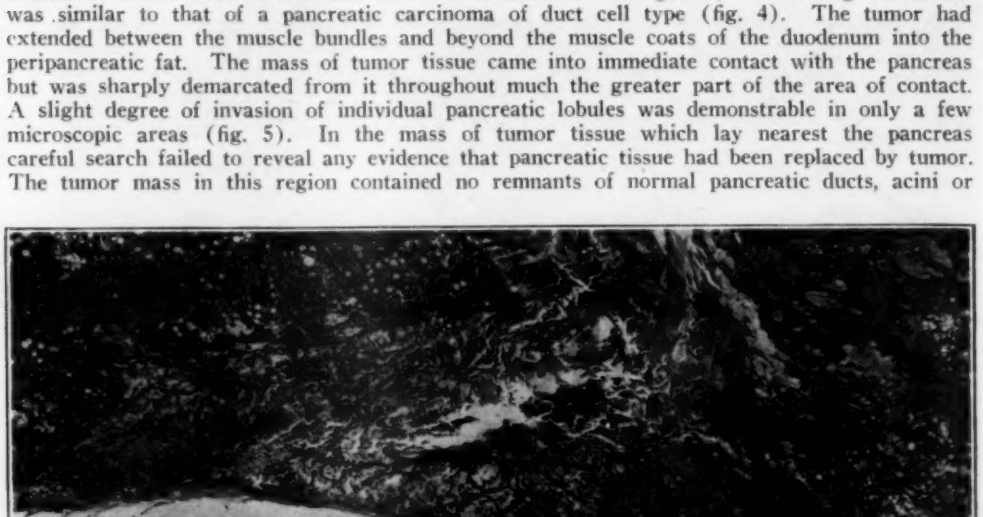


Fig. 5.—Low power photomicrograph showing the retroperitoneal tumor mass (above) impinging on the pancreas (below). The line of demarcation between the two is distinct throughout most of this field, although one pancreatic lobule is slightly infiltrated by the tumor.

islets of Langerhans. Thus, while the histologic structure of the tumor suggested an origin from pancreatic tissue, no evidence could be obtained from either the gross or the microscopic examination that it had originated in the pancreas itself. On the contrary, both the gross and the microscopic features of the tumor indicated an origin in the wall of the duodenum, but the structure was not that of a tumor originating from intestinal mucosa. This anomalous situation could be explained only by assuming that the tumor originated from aberrant pancreatic tissue in the duodenal wall.

The metastatic nodules showed neoplastic epithelial cells identical in character with those of the primary growth, but duct formation was rather more conspicuous in the metastases. The subcutaneous nodules were neurofibromas.

The diagnosis was: primary carcinoma of the infra-ampullary portion of the duodenum; secondary carcinoma of the omental and mesenteric lymph nodes, retroperitoneal fat (peripancreatic) and peritoneum; emaciation; acute bronchopneumonia; multiple neurofibromatosis; arteriosclerosis of aorta and coronary arteries (minimal).

COMMENT

The case of carcinoma of the infra-ampullary portion of the duodenum here reported conformed in the main to the typical clinical history as outlined in the introduction of this paper. There was epigastric distress with anorexia, persistent vomiting and rapid loss of weight. However, no epigastric mass was palpable at any time during the course of the illness, which was of seven and one-half months' duration.

The roentgenologic features in our case were entirely typical. There was an irregular filling defect involving the third portion of the duodenum with a concentric narrowing of the duodenal lumen and dilatation of the duodenum proximal to the area of narrowing. The normal pattern of the valvulae conniventes was obliterated in the area of the filling defect. A localized collection of barium lay in a large ulcer crater in the area of defect without evidence of any sinus tract passing external to the duodenal lumen. Moreover, the tenderness on palpation corresponded in position to the visualized abnormalities.

A number of other pathologic entities may exhibit roentgenologic abnormality which could simulate the evidence in this case in one or more respects. Invasion of the duodenal walls by a carcinomatous extension from the pancreas would be difficult to differentiate, but ulceration within the duodenal lumen without sinus tract formation extending external to the lumen would be unusual. Invasion of the duodenum by a carcinoma of the stomach should be differentiated by demonstration of the gastric lesion. Paraduodenal adhesions could cause obstruction with resultant dilatation of the proximal duodenum, but an extensive filling defect with ulceration would not be expected. Similar comment would also apply to the change produced by an unusual overgrowth of the head of the pancreas. A large impacted intraduodenal gallstone, a foreign body or a benign duodenal tumor might cause a local filling defect and a duodenal dilatation, but the duodenal lumen should be widened at the level of the filling defect rather than narrowed, and deep ulceration is not usual. Pressure defects from an extrinsic tumor, without invasion of the duodenal walls, would not produce a concentric narrowing of the lumen, an obliteration of the pattern of the valvulae conniventes or an ulceration within the duodenum. Sarcoma of the duodenum cannot be differentiated from carcinoma by roentgen examination. For these reasons, the opinion was expressed that the gross lesion demonstrated in this case was due to a primary neoplasm of the third portion of the duodenum.

We believe that only by the correct appreciation of the gross pathologic changes seen in the reported cases of primary duodenal cancer and by a painstaking roentgenoscopic search and study of correctly postured roentgenograms can a correct interpretation of the roentgen findings be made. In the first case cited by Bergendal,[5a] it was only at the third examination that the localization of the lesion was accomplished. Then the opinion was offered that the demonstrated gross filling defect with ulceration was consistent with the findings to be expected in cancer of the third portion of the duodenum. The more recent technical improvements of roentgen apparatus, particularly the addition of facilities for making serialographic film studies at the time of fluoroscopic examination, should improve the study of the duodenum in its entirety.

This case presented the gross pathologic features most frequently described as associated with infra-ampullary carcinoma of the duodenum. The tumor was scirrhous and annular in type. It had almost completely occluded the lumen of the duodenum, producing marked dilatation of the stomach and the proximal portion of the duodenum with hypertrophy of their walls. Ulceration was also present.

The histologic structure of the tumor in our case closely resembled that of a duct cell carcinoma of the pancreas. Similar observations in cases of primary carcinoma of the duodenum have been made by others, who have hinted at the possibility that carcinoma of the duodenum may arise from aberrant pancreatic tissue. The occurrence of such aberrant tissue is not uncommon. Faust and Mudgett [12] collected from the literature 369 cases and added 1 case of their own. Their analysis of the distribution of aberrant pancreatic tissue showed that it was located most frequently in the wall of the duodenum (30 per cent), stomach (26 per cent), jejunum (18 per cent) or ileum (13 per cent). Other rarer sites included the gallbladder, spleen, mesentery and omentum. In the last 1,970 autopsies performed in the department of pathology of McGill University, we have found 21 instances of aberrant pancreatic tissue, an incidence slightly greater than 1 per cent. Of these, 17 occurred in the duodenum, 3 in the jejunum and 1 in the stomach.

In spite of the relatively frequent occurrence of aberrant pancreatic tissue, the idea that carcinoma could originate in such pancreatic rests was scoffed at by Bland-Sutton,[13] who stated that there was no evidence to support such a theory. He admitted, however, that pathologists are not devoid of imagination. Nevertheless, the diagnosis of a malignant tumor originating in aberrant pancreatic tissue has been made by no less an authority than W. H. Welch. Jefferson [14] in 1916 reviewed a case in which the pathologic report was made by Professor Welch, who found a malignant adenoma of the pylorus arising in misplaced pancreatic tissue. More recently, Schmidt [15] described an adenoma of pancreatic tissue located in the upper part of the jejunum. Bookman [16] found a disklike tumor in the first portion of the duodenum which had no connection with the pancreas but which on histologic examination proved to be a carcinoma of pancreatic tissue. Vecchi [17] some years ago reported a large islet cell tumor which he described as a malignant adenoma arising in accessory pancreatic tissue located near the tail of the pancreas. Recently, Ballinger [18] reported a case of carcinoma of the pancreas of islet cell type arising in aberrant pancreatic tissue in the liver. Widespread metastases were present but no tumor tissue was found in the pancreas itself.

It is obvious that reports of benign and malignant tumors which have originated in aberrant pancreatic tissue are relatively few. However, there is no reason to doubt that tumors could arise from such misplaced tissue. Indeed, it might be supposed that such aberrant tissue, when it occurs, would be more likely to give origin to neoplasia than would the tissue of the pancreas itself. In the case here reported, there could be no doubt that the tumor arose in the wall of the duodenum, since this was the only structure from which a carcinoma could arise that was actually occupied by the tumor. The uncinate process of the pancreas was displaced rather than replaced by the tumor mass, and between the two there was grossly visible a sharp line of demarcation. It is true that the earliest beginnings of invasion of a few pancreatic lobules were demonstrated microscopically along this line, but apart from this the pancreas was completely free of tumor. On these grounds, the possibility of origin of the tumor from the pancreas as such was abandoned. In the duodenal wall the greatest mass of tumor tissue lay in the

12. Faust, D. B., and Mudgett, C. S.: Ann. Int. Med. **14**:717, 1940.
13. Bland-Sutton, J.: Tr. M. Soc. London **38**:1, 1914.
14. Jefferson, G.: Brit. J. Surg. **4**:209, 1916.
15. Schmidt, H.: Centralbl. f. allg. Path. u. path. Anat. **31**:497, 1921.
16. Bookman, M. R.: Ann. Surg. **95**:464, 1932.
17. Vecchi, A.: Arch. per le sc. med. **38**:277, 1914.
18. Ballinger, J.: Hypoglycemia from Metastasizing Insular Carcinoma of Aberrant Pancreatic Tissue in Liver, Arch. Path. **32**:277 (Aug.) 1941.

submucosa, elevating the mucosa, which, however, was intact and essentially normal over a considerable area. The mucosa terminated abruptly at the margins of the area of ulceration without showing any neoplastic or even hyperplastic changes, and there was a definite lack of continuity between the duodenal epithelium and the epithelial cells of the tumor around the margins of the ulcer at all points examined. Not only was the lack of connection between the duodenal mucosa and the tumor mass beneath it inconsistent with the assumption of origin of the latter from the former, but the histologic structure of the tumor was not that of a tumor arising from intestinal mucosa. Its structure was typically that of a duct cell carcinoma of the pancreas. These apparently inconsistent observations could be brought into complete harmony only by the assumption that the tumor arose from aberrant pancreatic tissue in the wall of the duodenum. Indeed, the location, the manner of spread and the gross and microscopic appearance of the tumor were precisely what one might expect of a carcinoma originating from misplaced pancreatic tissue in the submucosa or between the muscle layers of the duodenum and spreading from this site of origin inward toward the lumen and outward into the surrounding retroperitoneal fat. It was concluded, therefore, that the carcinoma originated in the duodenum, not, however, from the duodenal mucosa but from aberrant pancreatic tissue embedded in its wall.

SUMMARY AND CONCLUSIONS

The clinical, roentgenologic and pathologic features of primary carcinoma of the infra-ampullary portion of the duodenum as described in the literature are briefly reviewed. An additional case is presented. This occurred in a 35 year old man who had a typical clinical history. The roentgenologic diagnosis of neoplasm of the infra-ampullary portion of the duodenum was made preoperatively. The tumor presented the usual gross features of primary carcinoma of the duodenum located in the infra-ampullary portion, while its microscopic appearance suggested an origin from pancreatic tissue. The occurrence of pancreatic rests in the duodenum and elsewhere is much more frequent than is generally suspected, and it is suggested that such rests of pancreatic tissue may give rise to benign or malignant tumors, as has been reported in several instances. From the gross and microscopic appearance of the duodenal tumor in the case here reported, the conclusion was drawn that it was a carcinoma arising in aberrant pancreatic tissue in the infra-ampullary portion of the duodenum.

THERAPEUTIC TRENDS AND OPERATIVE MORTALITY IN CASES OF OBSTRUCTIVE JAUNDICE

LIEUTENANT ALEX W. ULIN
MEDICAL CORPS, ARMY OF THE UNITED STATES

The preoperative and postoperative management of patients with obstructive jaundice has evolved from a series of therapeutic contributions, each of which was in particular vogue for a period. The integral analysis of these methods is instructive, for it indicates the present trend, and forms a sounder basis not only for a modern therapeutic regimen but for further clinical and laboratory investigation. The factors that govern mortality in patients with obstructive jaundice and the philosophy of treatment that is soundest today are known to all. After synthetic vitamin K (menadione) and various related substances had been used parenterally for over one year with excellent results in the control of postoperative bleeding, the impression was obtained that at last the problem of the jaundiced patient undergoing surgical treatment, was under control.[1] This impression was not entirely correct. Indeed, mortality reports from other clinics often indicated no better, and perhaps poorer, results than in the era before the use of vitamin K. It is clear now that although vitamin K has reduced the incidence of postoperative bleeding the hard learned lessons of the period prior to the introduction of vitamin K appear to have been too often ignored in practice. By now it seems just as unreasonable to rely entirely on vitamin K in preparing jaundiced patients for operation as to rely on insulin alone in the treatment of diabetic acidosis. After its spectacular advent in this hospital it was learned that vitamin K is not the sine qua non, but an adjunct in treatment, along with diet, transfusions of blood and plasma and other measures. To emphasize this thesis, I wish to present the experience at this clinic for the last three years.

It is worth while to reconsider, as a background to this report, the therapy prior to the introduction of vitamin K. In disease of the gallbladder with obstruction of the common duct, the following mortalities have been reported: Mayo [2] (1920), over 15 per cent; Walters [3] (1923), 10 per cent; de Takáts [4] (1924), 30 per cent; Ravdin, Rhoads, Frazier and Ulin [5] (1938), 14 per cent, and Illingworth [6] (1939), 11 per cent; Hunt [7] reported an operative mortality of 31 per cent among patients with carcinoma of the pancreas. The recent reports have made much of the

Read at a seminar meeting, Feb. 7, 1942.
From the Department of Surgery of the College of Medicine, University of Cincinnati, and the Cincinnati General Hospital, Cincinnati, Ohio.

1. Stewart, J. D.: Clinical and Experimental Evidence on the Nutritional Requirements in Obstructive Jaundice, New England J. Med. **223**:1059, 1940.
2. Mayo, C. H.: Jaundice: Surgical Significance, Surg., Gynec. & Obst. **30**:545, 1920.
3. Walters, W.: Physiologic Considerations in the Treatment of Obstructive Jaundice, J. A. M. A. **87**:2153 (Dec. 25) 1926.
4. de Takáts, G.: Some Problems of Jaundice and Their Significance in Surgery, Ann. Surg. **79**:662, 1924.
5. Ravdin, I. S.; Rhoads, J.; Frazier, W., and Ulin, A. W.: The Effect of Recent Advances in Biliary Physiology on the Mortality Following Operation for Common Duct Obstruction, Surgery **3**:805, 1938.
6. Illingworth, C. F. W.: Hemorrhage in Jaundice, Lancet **1**:1031, 1939.
7. Hunt, V. C.: Surgical Management of Carcinoma of the Ampulla of Vater and of the Periampullary Portion of the Duodenum, Ann. Surg. **114**:570, 1941.

incidence of bleeding and the prothrombin time; relatively infrequent is a full report on operative mortality. At the outset, therefore, it would be well to define the bases for my analysis. By jaundice I mean primarily obstructive jaundice. I am interested in the patients who are clinically jaundiced at the time of operation. The death of any patient who died by the thirtieth postoperative day, regardless of cause, or who died as a direct result of the operative procedure regardless of time, is considered an operative death. One further qualification seems obvious. The seriousness of this particular illness will vary in different localities.[8] The more seriously ill patients, clinically almost moribund and with far advanced pathologic changes, will be found in a charity institution like the Cincinnati General Hospital. The percentage of malignant lesions in the total number of cases and the type of operation must also be kept in mind.

Postoperative hemorrhage has since 1891 been recognized as an important cause of operative death of patients with obstructive jaundice.[9] In the past two decades, trends of therapy have been guided by investigations into the clotting defect as well as by studies of hepatic pathology and physiology. In 1926 Walters [3] emphasized the fact that with obstruction of the biliary tract there is impairment of hepatic function from the very beginning. Even with simple disease of the gallbladder, extensive hepatitis may exist,[10] and in such circumstances quantitative studies of the bile often reveal hepatic disturbance before obstruction of the common duct occurs. The pathologic changes in the liver produced by obstruction in the biliary tree were demonstrated by Counsellor and McIndoe.[11] They described the pathogenesis of so-called hydrohepatosis. MacCallum [12] emphasized the factors of infection and back pressure. Finally there was described the picture of fatty accumulation in the hepatic cell in the presence of obstruction of the liver.[13]

The question of hepatic lipid is coming more and more to the fore as a pathophysiologic problem. The first attempt to solve it clinically was with administration of carbohydrate. This idea of carbohydrate therapy, glycogenesis and the significance of hepatic glycogen in relation to injury of the liver arose from the concepts promulgated by Rosenfeld in 1900.[14] He indicated the reciprocal relationship between hepatic glycogen and hepatic lipid. In this country in 1915, Opie and Alford [15] first reported experiments on animals and worked out protocols in regard to study of the composition of the liver in relation to diet and toxins. They found that a high carbohydrate diet conditioned the livers of experimental animals to withstand exposure to chloroform, whereas a high fat diet induced a singular susceptibility to such exposure. In 1926 Walters [3] stated that at the Mayo Clinic patients with obstructive jaundice were given a high carbohydrate diet, supplemented with

8. Ravdin, I. S.: Surgical Problems of Jaundice, J. M. Soc. New Jersey **23**:341, 1926.

9. (*a*) Ivy, A. C.; Shapiro, P. F., and Melnick, P.: Bleeding Tendency in Jaundice, Surg., Gynec. & Obst. **60**:781, 1935. (*b*) Walters, W.: Treatment of Obstructive Jaundice and Its Complications, California & West. Med. **29**:77, 1928.

10. (*a*) Ravdin, I. S.: Surgical Diseases of the Extrahepatic Bile Ducts, New England J. Med. **220**:326, 1939. (*b*) Boyce, F.: The Role of the Liver in Surgery, Springfield, Ill., Charles C Thomas, Publisher, 1941, p. 37.

11. Counsellor, V. S., and McIndoe, A. H.: Dilatation of Bile Ducts, Surg., Gynec. & Obst. **43**:729, 1926.

12. MacCallum, W. G.: Obstructive Biliary Cirrhosis, in Text Book of Pathology, ed. 6, Philadelphia, W. B. Saunders Company, 1936, p. 315.

13. Schnedorf, J. G., and Orr, T. G.: Fifty-Two Proven Cases of Carcinoma of the Pancreas and Ampulla of Vater, with Special Reference to Fatty Infiltration of the Liver, Ann. Surg. **114**:603, 1941. Ravdin, Rhoads, Frazier and Ulin.[5]

14. Rosenfeld, G.: Fettbildung, Ergebn. d. Physiol. **2**:50, 1903.

15. Opie, E. L., and Alford, L. B.: The Influence of Diet on Hepatic Necrosis and Toxicity of Chloroform, J. A. M. A. **62**:895 (March 21) 1914.

dextrose when necessary. Ravdin, Riegel and Morrison [16] reported that clinically dextrose exerts a protective action if the liver is not injured beyond a certain degree of repair. In 1932 Cowan and Wright [17] reported that the damaged liver rapidly takes up intravenously administered dextrose. Recently Ravdin [18] and later Stewart [1] well reviewed the problem of metabolism associated with the pathology and physiology of the liver.

As for the postoperative hemorrhage of jaundiced patients, it is no longer believed that a quantitative deficiency in the blood calcium is responsible.[19] In 1930, calcium was still in vogue as the one specific single prophylactic agent used in preparing jaundiced patients for operation.[5] The work of Cowan and Wright,[17] of Ravdin, Riegel and Morrison [16] and of Cantarow, Dodek and Gordon [20] seemed to indicate that there is some relation between dextrose metabolism, hepatic function and calcium. All of these investigators suggested that obstructive jaundice is associated with a disturbance in some phase of that relationship. As late as 1938, Walters [21] still believed that calcium is beneficial. Apparently it is most indicated when hypoproteinemia is present.

The history of the significant therapeutic periods, as outlined by Ravdin, Rhoads Frazier and Ulin,[5] reveals that prior to 1929 preoperative preparation was little stressed. Great reliance was placed on the use of calcium and postoperative blood transfusions were given only occasionally. By 1929 the clinicians closed the gap between practice and experimental evidence indicating the importance of hepatic function in cases of obstructive jaundice. I need only mention the advances made in appreciation and utilization of the principles of fluid and electrolyte balance. Transfusions were still given only occasionally and always postoperatively. Stress was placed on high carbohydrate diets supplemented with intravenous administration of dextrose. From 1933 to 1937 blood transfusion preoperatively as well as postoperatively became established, not only as the best means of combating the hemorrhagic diathesis but as an excellent general supportive measure. Furthermore, in 1935 Snell [22] reported that of 40 patients who died of chronic parenchymatous disease of the liver 80 per cent had edema of the pulmonary bases, terminal bronchopneumonia or hydrothorax. However, the pulmonary lesions were supposed to be terminal pneumonia, except that the edema of the alveolar walls was considered of possible significance. These observations Snell correlated with the discovery of anoxic anoxemia in patients with obstructive jaundice. For this reason, Judd, Snell and Hoerner [23] subsequently emphasized the importance of

16. Ravdin, I. S.; Riegel, C., and Morrison, J. L.: Coagulation of Blood: Comparative Value of Calcium and Glucose in Decreasing Clotting Time, Ann. Surg. **91**:801, 1930.

17. Cowan, D. W., and Wright, H. N.: The Interrelationship Between Blood Sugar, Blood Calcium and Blood Coagulability, Am. J. Physiol. **100**:40, 1932.

18. Ravdin, I. S.: (*a*) The Protection of the Liver from Injury, Surgery **8**:204, 1940; (*b*) Progress in the Pre-Operative and Post-Operative Care of Patients with Lesions of the Biliary Tract, Bull. New York Acad. Med. **17**:500, 1941.

19. Gunther, L., and Greenberg, D. M.: The Diffusible Calcium and Proteins of Blood Serum in Jaundice, Arch. Int. Med. **45**:983 (June) 1930. Linton, R. R.: Relation of Calcium to the Hemorrhagic Tendency in Obstructive Jaundice, Ann. Surg. **93**:707, 1931. Wangensteen, O. H.: Hemorrhagic Diathesis of Obstructive Jaundice and Its Treatment, ibid. **88**:845, 1928. Ravdin, Riegel and Morrison.[16]

20. Cantarow, A.; Dodek, S. M., and Gordon, B.: Calcium Studies in Jaundice, Arch. Int. Med. **40**:129 (Aug.) 1927.

21. Walters, W., in discussion on Butt, Snell and Osterberg.[25]

22. Snell, A. M.: Chronic Liver Disease: Its Effect on the Blood, Ann. Int. Med. **9**:690, 1935.

23. Judd, E. S.; Snell, A. M., and Hoerner, M. T.: Transfusion for Jaundiced Patients, J. A. M. A. **105**:1653 (Nov. 23) 1935.

administration of oxygen and transfusion of blood as measures to increase the arterial saturation of oxygen in persons with obstructive jaundice.

The more important therapeutic measures that were evolved before the introduction of vitamin K [24] may be summarized as giving of calcium, use of a high carbohydrate diet, oral and intravenous administration of dextrose, attention to fluid intake and electrolyte balance, transfusion of blood, administration of oxygen, better choice and use of anesthetics, preoperative observation over longer periods of time, waiting for a decrease in the level of bilirubin in the blood, evaluation of any existing complications, use of bile preparations, and finally gradual postoperative decompression of the biliary system.[5] Although the incidence of bleeding remained the same, mortality due to hemorrhage and operative mortality were halved. Ravdin, Rhoads, Frazier and Ulin [5] in 1938 reported a mortality of 2 per cent due to hemorrhage and a total operative mortality of 9 per cent. Judd, Snell and Hoerner [23] reported an operative mortality of 4 per cent in 1935. The most evident improvement occurred subsequent to 1929, coincident with the increased use of dextrose and high carbohydrate diets and parenteral administration of fluids. By 1933, when the use of preoperative transfusion had become established, the best mortality figures for the decade were in the making.

Thus it may be seen that by 1937, although the fundamental fault in the coagulative mechanism in the blood of jaundiced patients was not generally understood, a therapeutic regimen had been elaborated that gave relatively good results. In commenting on the report of Butt, Snell and Osterberg [25] on the use of vitamin K at the Mayo Clinic, Walters [21] pointed out that mortality due to hemorrhage had been low at the clinic even before the use of vitamin K. His figure of 5 per cent for 400 operations performed during 1936-1937 suggests an apparently rosier picture than exists at most clinics. But that is a report not for total operative mortality but for mortality due to hemorrhage. At any rate, the system of therapy previously described had reduced the mortality but not the incidence of bleeding. It appeared that the discovery of the cause of bleeding and the rectification of this physiologic defect would be the final answer to the problem of operative mortality.

The tremendous interest and effort of investigators along this line were soon to bear results.[26] It was the correlation of disconnected observations spread over a decade that eventually gave the solution and culminated in the use of vitamin K in the hemorrhagic diathesis of patients with obstructive jaundice. By 1939 the isolation of concentrated, supposedly pure vitamin K had been achieved, to be followed by the synthesis of substances with vitamin K activity and the initiation of parenteral therapy.[27] As for the administration of vitamin K, Butt, Snell and Osterberg [25] in 1938 urged the preoperative classification of jaundiced patients as to hazard. With such patients a preoperative determination of prothrombin time is probably as important as any test of hepatic function. Even when prothrombin time was normal Butt, Snell and Osterberg insisted on prophylactic therapy with

24. Ravdin, I. S., and Johnston, C. G.: The Hemorrhagic Tendency of Obstructive Jaundice, Am. J. M. Sc. **193**:278, 1937. Ravdin.[8]

25. Butt, H. R.; Snell, A. M., and Osterberg, A. E.: Further Observations: Use of Vitamin K in Hemorrhagic Diathesis in Cases of Jaundice, Proc. Staff Meet., Mayo Clin. **13**:753, 1938.

26. Dam, H.: Fat-Soluble Vitamins: Vitamin K, in Luck, J. M., and Smith, J. H. C.: Annual Review of Biochemistry, Stanford University, Calif., Annual Reviews, Inc., 1940, vol. 9, p. 362. Quick, A. J.: Prothrombin in Hemophilia and in Obstructive Jaundice, J. Biol. Chem. **109**:lxxiii, 1935. Opie and Alford.[15]

27. (*a*) Norcross, J. W., and McFarland, M. D.: Intravenous Use of 2-Methyl-1,4-Naphthoquinone in Hypoprothrombinemia, J. A. M. A. **115**:2156 (Dec. 21) 1940. (*b*) Stewart, J. D.: Oral and Parenteral Use of Synthetic Vitamin K Active Substances in Hypoprothrombinemia, Surgery **9**:212, 1941.

vitamin K. Postoperatively, they followed their patients with prothrombin determinations for eight days. Ordinarily, vitamin K could well be given orally. But when values of prothrombin approach the critical level or there is actual bleeding, they as well as others (Norcross and McFarland,[27a] Stewart,[28] Stewart and Rourke,[29] Ravdin [18b] and Coller and Farris [30]) have advised parenteral administration. The majority of the clinicians have found intravenous administration the most effective and rapid method of lowering the prothrombin time to normal. Today it is generally agreed that failure to respond to parenterally administered vitamin K can be considered as an ominous prognostic sign. Can the prothrombin time itself and the response to vitamin K therapy be used as a test of hepatic function? Ziffren, Owen, Warner and Peterson [31] recently discussed this point and, apparently using the finer laboratory method of Warner and his associates,[32] showed that variations in prothrombin time can be readily disclosed and may be a reliable indication of hepatic function, at least as far as prothrombin is concerned.

The reports on the use of vitamin K indicate rather uniform success in reducing the incidence of postoperative hemorrhage. Figures for operative mortality are incomplete, but there appears to be no remarkable improvement. Butt, Snell and Osterberg [25] (1938) reported 3.1 per cent for 64 cases; Rhoads [33] (1939), 8.1 per cent for 12 cases, and Illingworth [6] (1939), 8.5 per cent for 14 cases. Stewart [28] (1939) gave no mortality figure for 27 cases but stated that 7 patients had massive postoperative bleeding. Stewart [27b] (1941) gave 20 per cent as the operative mortality for 20 cases. All these reports are for cases in which vitamin K was given orally. In 1941, after using subcutaneous injections of a synthetic substance with vitamin K activity (the sodium bisulfite derivative of methyl naphthoquinone) in the treatment of 14 patients, Stewart [27b] reported an operative mortality of 7 per cent. Norcross and McFarland [27a] (1940) who used intravenous injections of synthetic vitamin K (menadione) did not report mortality, but from their table it appears that for the 15 cases in which operation was done there was an operative mortality of 20 per cent. Hunt [7] (1941) reported a 21 per cent mortality for cases of carcinoma of the pancreas. In 1941 operative mortality for cases of obstructive jaundice was 19 per cent in the Cincinnati General Hospital.

Although in 1939 and 1940 the opinion prevailed that the case in which hypoprothrombinemia due to obstructive jaundice would not respond to K was rare, it appears now that this is not true. Every author has a failure or two to report, though the total number of such failures in any series is usually small. To some extent it appears that perhaps too much reliance has been placed on vitamin K. As Walters [21] pointed out, one must not forget the lessons learned before the introduction of vitamin K therapy. Obviously, its intrinsic value has been more than that of a weak prosthetic to a defective prothrombin mechanism. However, the use

28. Stewart, J. D.: Prothrombin Deficiency and the Effects of Vitamin K in Obstructive Jaundice and Biliary Fistulae, Ann. Surg. **109**:588, 1939.

29. Stewart, J. D., and Rourke, G. M.: Control of Prothrombin Deficiency in Obstructive Jaundice by Use of Vitamin K, J. A. M. A. **113**:2223 (Dec. 16) 1939.

30. Coller, F. A., and Farris, J. M.: The Management of the Jaundiced Patient with Special Reference to Vitamin K, Surg., Gynec. & Obst. **73**:21, 1941.

31. Ziffren, S. E.; Owen, C. A.; Warner, E. D., and Peterson, F. R.: Hypoprothrombinemia and Liver Function, Surg., Gynec. & Obst. **74**:463, 1942.

32. Smith, H. P.; Warner, E. D., and Brinkhous, K. M.: Prothrombin Deficiency and Bleeding Tendency in Liver Injury, J. Exper. Med. **66**:801, 1937. Warner, E. D.; Brinkhous, K. M., and Smith, H. P.: A Quantitative Study of Blood Clotting: Prothrombin Fluctuations Under Experimental Conditions, Am. J. Physiol. **114**:667, 1936.

33. Rhoads, J. E.: The Relation of Vitamin K to Hemorrhagic Tendency in Obstructive Jaundice, with a Report on Cerophyl as a Source of Vitamin K, Surgery **5**:794, 1939.

of vitamin K certainly does not obviate the use of blood.[34] Also, as was pointed out by Butt, Snell and Keys,[35] in cases of obstructive jaundice with damage to the liver the total protein in the blood may well be within normal limits, but because of a lowered albumin content and reversal of the albumin-globulin ratio, the colloid osmotic pressure may be low, so that the indication for plasma may be more urgent than it appears to be. Finally, even when vitamin K is administered parenterally there is indication for the use of bile for reasons other than that it promotes absorption of vitamin K from the intestinal tract.

Counsellor and McIndoe[11] doubted that the reserve of the liver would be overcome by even the most advanced obstructive hepatic syndrome. But to any one who has followed patients with obstructive jaundice and studied their livers at autopsy, this conclusion seems unreasonable. The unexpected appearance of

TABLE 1.—*Patients with Obstructive Jaundice Operated on*

	Patients	Deaths	Operative Mortality, per Cent
1939	14	5	36
1940	12	4	33
1941	16	3	19
Total	42	12	29

TABLE 2.—*Obstructive Jaundice Due to Carcinoma of the Head of the Pancreas*

	Patients	Deaths	Operative Mortality, per Cent
1939	8	4	50
1940	4	2	50
1941	8	1	13
Total	20	7	35

TABLE 3.—*Patients with Obstruction of the Common Duct Not Due to a Malignant Growth*

	Patients	Deaths	Operative Mortality, per Cent
1939	6	1	17
1940	8	2	25
1941	8	2	25
Total	22	5	23

hemorrhage postoperatively, the conviction that many elderly patients and many patients in whom the obstructive syndrome is superimposed on such a pathologic condition as cirrhosis or malignant metastases receive a knockout blow from operative trauma and anesthesia, and now the lack of response to vitamin K of about 10 per cent of all these patients with obstructive jaundice seem conclusive evidence that the liver is far from inexhaustible in its performance and is not invulnerable to trauma, toxemia and anoxia.

In the light of the foregoing discussion, the record of the 42 patients with jaundice operated on in this clinic in the past three years can now be examined. Forty-eight per cent of the obstructions of the common duct were due to malignant tumors. I discarded many cases of stone in the common duct because of inadequate

34. Karabin, J. E.; Udesky, H., and Seed, L.: Effect of Stored Citrated Blood Transfusion upon Patients with Hypoprothrombinemia, Surg., Gynec. & Obst. **73**:10, 1941.

35. Butt, H. R.; Snell, A. M., and Keys, A.: Plasma Protein in Hepatic Disease: Study of Colloid Osmotic Pressure of Blood Serum and of Ascitic Fluid in Various Diseases of the Liver, Arch. Int. Med. **63**:143 (Jan.) 1939.

data concerning jaundice. None of the cases from the private services was considered. It is not absolutely important to compare mortality figures with those from other hospitals; it is important, however, to watch the mortality in any given clinic from year to year. According to the standards of selection that have been set, it is now possible to scrutinize the results of therapy for the type of patient treated at the Cincinnati General Hospital (tables 1, 2 and 3).

Tables 4 and 5 show the types of operation that were done.

It will be seen that in 65 per cent of the cases of malignant disease a major palliative operation was performed. The patients who had had only an exploratory laparotomy were of course the sickest, and no special effort was made postoperatively to prolong their life.

The figures show that although in 1941 about 50 per cent of the patients had malignant growths and about the same type of major surgical procedure was being done on all, the operative mortality was distinctly lower. In cases of malignant tumor a reduction from 50 per cent to 13 per cent was achieved. As

TABLE 4.—*Operations Performed on Twenty Patients with Obstruction of the Common Duct Due to a Malignant Tumor*

	Patients	Died	Mortality, per Cent
Exploratory laparotomy and biopsy	7	3	43
Palliative (cholecystgastrostomy, etc.)	6	2	33
Whipple operation (3 patients had first stage only)	7	2	29
Total	20	6	35

TABLE 5.—*Operations Performed on Twenty-Two Patients with Obstruction of the Common Duct Not Due to a Malignant Growth*

	Patients	Died	Mortality, per Cent
Cholecystectomy and exploration and drainage of common duct	17	3	18
Exploration and drainage of common duct	2	0	0
Cholecystgastrostomy	2	2	100
Choledochoduodenostomy	1	0	0
Total	22	5	23

far as age, debilitation, diabetes and pulmonary and nephritic complications are concerned the 1941 patients, if not sicker than usual, were the ordinary run. Consequently, there arise certain pointed questions concerning our preoperative and postoperative therapy. These questions and their answers had been considered in 1940 with apparent beneficial results.

How was vitamin K given, and what response was obtained? The response to oral and parenteral administration was satisfactory. In the majority of cases the degree of jaundice was measurable by an icteric index of from 40 to 100. In only 2 cases was the prothrombin time, on admission, within normal limits. However, there was a preoperative record of this test in only 30 cases. Response to vitamin K was indicated by a return of prothrombin time to normal. Quick's method of determining prothrombin time was used.

Thirteen per cent of the patients treated did not respond Two of these patients definitely did not receive adequate oral doses of the vitamin or of bile salts. In 1941 such excellent response was obtained from intramuscular administration that vitamin K was given intravenously in few instances. In using vitamin K [36]

36. The preparation used was klotogen (Abbott Laboratories). Each capsule contains 1,000 units of vitamin K as measured by the modified Almquist method.

orally our best results were obtained with capsules containing a concentrate of the vitamin in peanut oil and bile salts. Three to six of the capsules were given per day, and 2 Gm. of bile salts. The following is an example of reductions in prothrombin time (Quick) after two to three days of oral administration of vitamin K; patient G. K., twenty-five seconds to fourteen seconds; patient C. M. nineteen seconds to twelve seconds; patient G. L. seventy-six seconds to fifteen seconds.

In 1940 there was no postoperative hemorrhage. Vitamin K was being given more correctly, i. e., in larger doses of better preparations; blood transfusions were again being given preoperatively. At this time it was realized that, although vitamin K was being used successfully, operative mortality had not improved. Some of the more significant errors in our preoperative handling are listed as follows:

1. Too much emphasis was placed on tests of prothrombin time and of response to vitamin K as opposed to other tests of hepatic function, and clinical impressions were not sufficiently considered.

2. Vitamin K was prescribed in a haphazard fashion, with no plan for the specific needs of the patient. One patient who did not respond to intramuscular injections did not receive vitamin K intravenously.

TABLE 6.—*Response to Administration of Vitamin K*

Year	Patients	Oral	Intramuscular	Intravenous	No Response	Postoperative Bleeding
1939	10	10	0	0	2	4
1940	9	6	2	1	2	0
1941	11	0	9	2	1	1
Total	30	..	..	..	5	

3. Such forms of supportive therapy as blood transfusion and administration of bile and of oxygen, which used to be mainstays, were amazingly neglected.

4. The preoperative stay in the hospital was unusually short. Too often the patient was taken from the medical wards to the operating room. One normal value for prothrombin time following good response to vitamin K was considered to be sufficient evidence that the patient was ready for operation.

5. Postoperatively, the patient was not followed carefully enough, with determinations of prothrombin time.

6. Study of high carbohydrate, high protein and low fat diets and diets designed for the person with disease of the gallbladder revealed that those prescribed in the Cincinnati General Hospital were hardly suitable for the jaundiced patient. Too often they were high in caloric value and nothing more. The interns sent a routine requisition to the dietary department, where it was filled without an understanding of the individual problem. For instance, the most popular diet, called high carbohydrate, high protein, furnished 3,800 calories and consisted of 38 per cent carbohydrate, 42 per cent fat and 20 per cent protein, a far cry from the diet recommended by Ravdin.

7. Vitamin K seemed to have displaced other vitamins, such as vitamin C and the members of the B complex, from the order sheets.

8. Finally, no one person was interested in critical scrutiny of all the jaundiced patients, both as to administration of a therapeutic plan and study of the results.

In 1941, by rehabilitating all the measures proved effective before the introduction of vitamin K and by establishing a plan of vitamin K therapy according to the recommendations of Snell, we did far better. Even then, because the plan

was not rigidly adhered to, one patient who was not followed carefullly had postoperative bleeding and subsequently died. In 1941, the average preoperative period in the surgical ward was seven days. My associates and I, made out the diets, to the last detail, in cooperation with the dietitians. We educated them to our problem and as far as necessary individualized the diets to meet the obvious practical problems. Thus, in 1940 the problem of hemorrhage was solved by the proper use of vitamin K, as it was in all other clinics. But not until now have I felt that the sum of our treatment made an intelligent answer to the problem of operative mortality in the jaundiced patient.

Could response to vitamin K as measured by the Quick test be used as a test of hepatic function? No response or a poor response is of gloomy prognostic significance. In 4 of the 5 patients who did not respond, hemorrhage was the major clinical cause of death. Two of our patients, H. H. and E. F., responded well to oral administration of vitamin K. At autopsy, both showed extensive damage to the liver. Clinically, the death of H. H. was due to hepatic failure. On the other hand, G. W., a patient operated on this year (and not included in the series), showed no response to intravenously administered vitamin K. Her progressively downhill course forced a decision; she was operated on and made an uneventful recovery with no evidence of postoperative bleeding. I can now recall the isolated cases reported by Illingworth, Butt and others, in which very low levels of prothrombin were not accompanied by postoperative hemorrhage. Coller and Farris [30] concluded that patients with severe hepatic damage that do not respond to vitamin K are rare. Ziffren's [31] report indicated some correlation between results of prothrombin tests, hepatic function and prognosis. However, the literature and my experience lead to equivocal conclusions. Again, all I can say is that prothrombin and tests for prothrombin as known today are not by any means the whole story in cases of obstructive jaundice.

The failure of vitamin K wholly to solve the problem of operative mortality once more focused attention on hepatic pathology and physiology. Recently Schnedorf and Orr [13] described extensive fatty changes seen in the liver in many patients with carcinoma of the head of the pancreas; they advised the clinical trial of certain lipotropic substances to correct the apparent fault in hepatic metabolism. In our cases we found the pathologic picture more complicated. Complete postmortem examinations were carried out on 8 of 12 patients who died. From another patient a specimen of the liver was obtained for biopsy. Examination of the structure and composition of the liver revealed that we were dealing mainly with fatty changes, necrosis, infection, sclerosis, degenerative changes in the hepatic cells themselves and malignant metastases. Of the 8 patients on whom autopsy was done, 100 per cent showed unquestioned pathologic changes in the lungs; 4 showed pathologic changes in the pancreas. Whereas clinically only 1 death was ascribed to hepatic failure, pathologically the liver was chiefly incriminated in 6 cases. Because of some toxicity, jaundice and postmortem changes significance cannot be attached to the pathologic changes observed in the pancreas.

In 1929 Ravdin and his co-workers [37] reported data derived from experiments on dogs in support of a newer concept of hepatic glycogen and lipids. They showed experimentally that a high protein as well as a high carbohydrate diet gives the best protection to the liver. Consequently, they have advocated the use of similar diets in the preparation of jaundiced patients for operation. Ravdin [18] advised an intake of at least 3,000 calories divided as follows: protein, 20 to 25 per cent; carbohydrate, 75 to 80 per cent; fat, less than 5 per cent. The use of interval

37. Ravdin, I. S.: Some Aspects of Carbohydrate Metabolism in Hepatic Disease, J. A. M. A. **93**:1193 (Oct. 19) 1929.

feedings, the preparation of individual diets (as for a diabetic) and the administration of crystalline vitamin B_1 are stressed. Doubt is cast on the intravenous use of dextrose, at least as a sole preoperative measure. Still Cowan and Wright [17] and in 1939 Soskin and Hyman [38] stressed the value of intravenous administration of dextrose in providing a strong immediate stimulus for glycogenesis. It also forms a means of providing carbohydrates for patients who are desperately sick and unable to take an adequate diet.

At this point, it is important to distinguish between damage to the liver and degeneration of the liver, between the sequelae of a single trauma to a healthy dog's liver and those of a persistent noxious process in a human liver, a process which itself may be superimposed on preexisting pathologic changes and have added to it finally the trauma of anesthesia and operation. How well will desperately sick jaundiced patients handle an excessive intake of protein? What proteins and what amino acids are best handled? Are any actually injurious? The lipotropic effect of certain sulfamino acids has been described by investigators.[39] Recently, however, cystine has been incriminated as a possible hepatotoxic substance.

In 1939 Dragstedt and his associates [40] advanced the theory of a pancreatic lipotrophic hormone called lipocaic, a fat-free pancreatic extract, small doses of which are effective in curing the fatty liver of pancreatectomized dogs. Although some amazing clinical results on fatty livers are reported in the literature on diabetes and on cardiac disease, lipocaic is still not recognized by the Council on Pharmacy and Chemistry.[41] It appears that the ordinary high protein diet for jaundiced patients will have to be modified in many respects.

SUMMARY

Trends in the treatment of jaundiced patients subjected to operation and their pathologic and physiologic basis are briefly and chronologically discussed.

Operative mortalities before and after the introduction of vitamin K are discussed. Vitamin K itself has not appeared to solve the problem of operative mortality in cases of obstructive jaundice. The reasons for failure are enumerated.

The results of 42 operations performed in the last three years are presented, with an analysis of the therapy, operative mortality and postmortem observations.

By the proper use of vitamin K, the problem of postoperative hemorrhage was solved; but it was only by the application of a complete therapeutic regimen that the operative mortality was significantly reduced.

Response to vitamin K as an index of hepatic function is discussed.

The pathologic changes in the liver are discussed. Some pathologic changes have been found in the pancreas, but their significance is doubtful.

38. Soskin, S., and Hyman, M.: Physiologic Basis of Intravenous Dextrose Therapy for Diseases of the Liver, Arch. Int. Med. **64**:1265 (Dec.) 1939.

39. Best, C. H.; Hershey, J. M., and Huntsman, M. E.: The Effect of Lecithin on Fat Deposition in the Liver of the Normal Rat, J. Physiol. **75**:56, 1932. Best, C. H.; Ferguson, G. C., and Hershey, J. M.: Choline and Liver Fat in Diabetic Dogs, ibid. **79**:94, 1933. Singal, S. A., and Eckstein, H. C.: The Lipotropic Action of Some Sulfur Containing Amino Acids and Related Substances, J. Biol. Chem. **140**:27, 1941.

40. Dragstedt, L. R.: The Present Status of Lipocaic, J. A. M. A. **114**:29 (Jan. 6) 1940. Dragstedt, L. R., and others, in discussion on Spellberg, M. A., and Keeton, R. W.: Influence of Various Substances on Fatty Livers Produced by Scorbutogenic Diets, ibid. **114**:519 (Feb. 10) 1940. Dragstedt, L. R.; Vermeulen, C.; Goodpasture, W. C.; Donovan, P. B., and Geer, W. A.: Lipocaic and Fatty Infiltration of the Liver in Pancreatic Diabetes, Arch. Int. Med. **64**:1017 (Nov.) 1939.

41. The Present Status of Lipocaic, report of the Council on Pharmacy and Chemistry, J. A. M. A. **115**:1454 (Oct. 26) 1940.

INFILTRATION OF BONE WITH SPONTANEOUS FRACTURE IN A CASE OF CHRONIC MYELOGENOUS LEUKEMIA

LEO M. MEYER, M.D.

ÁSA B. FRIEDMANN, M.D.
AND
VICTOR GINSBERG, M.D.
BROOKLYN

The bone marrow in leukemia is the seat of a diffuse hyperplastic process extending throughout all marrow-containing bones. The spongy trabeculae are destroyed, and the cortex of the long bones becomes thin. On microscopic examination the lesions in bone appear to be due to pressure and growth, local or diffuse, within the bone rather than to loss of blood supply. In some instances there is a direct extension of the leukemic process through the cortex, the periosteum being lifted by the formation of small subperiosteal tumor masses. These masses may extend into the surrounding soft tissues.

Roentgenograms of the skeleton of patients with leukemia show a variable picture. The bones involved in order of frequency are the pelvis, the lumbar vertebrae, the neck of the femur, the head of the humerus and the skull, and less often the metacarpal bones, the ulna, the tibia and the fibula. In the lymphatic leukemias osteoclastic and osteosclerotic changes are observed. In the myeloid type both osteolytic and osteosclerotic lesions have been described, with diffuse or localized areas of rarefaction or sclerosis. In both types of leukemia periostitis and periosteal elevation may be seen.

Craver and Copeland [1] studied 169 cases of leukemia, 86 of lymphatic and 83 of myelogenous. In 7 per cent of the cases in the former group osseous involvement was seen on roentgenographic examination. In only 1 of the cases of myelogenous leukemia was osseous involvement found. No fractures were observed.

In children the disease apparently involves the skeletal structures more frequently. Snelling and Brown [2] described 12 cases of lymphatic leukemia in patients under the age of 6 and found that in 8 there was rarefaction at the ends of the long bones and in 4 there were periosteal elevations. The following year Baty and Vogt [3] studied the roentgenograms of 60 children with leukemia and found that there was diminished density just proximal to the metaphyses of the long bones in 43 of them. In 2 there was periosteal elevation.

Forkner [4] reviewed case reports of osseous involvement up to 1938 and discussed the histopathologic picture. Since that date a paper has appeared on this subject by Mendl and Saxl,[5] who described 3 cases of leukemia in which there was roentgen evidence of involvement of bone.

From the Radiation Therapy Service, Kings County Hospital.

1. Craver, L. F., and Copeland, M. M.: Changes of the Bones in the Leukemias, Arch. Surg. **30**:639 (April) 1935.

2. Snelling, C. E., and Brown, A.: Bone Changes in Leukaemia: Clinical and Roentgenological, Arch. Dis. Childhood **9**:315, 1934.

3. Baty, J. M., and Vogt, E. C.: Bone Changes of Leukemia in Children, Am. J. Roentgenol. **34**:310, 1935.

4. Forkner, C. E.: Leukemia and Allied Disorders, New York, The Macmillan Company, 1938, p. 108.

5. Mendl, K., and Saxl, O.: Bone Changes in Leukemia, Am. J. Roentgenol. **44**:31, 1940.

In 1913 Pforringer [6] reported the first case of spontaneous fracture occurring in a patient suffering from lymphatic leukemia. A woman aged 50 sustained a fracture of one femur, followed a month later by fracture of the other femur while the patient was still confined to bed. At autopsy lymphatic leukemia was found. In 1931 Trusen [7] described the case of a child of 5 years who had severe anemia and leukopenia. The white cells numbered 2,800, of which 92 per cent were lymphocytes. The child was thought to have an acute aleukemic lymphatic leukemia. During the course of the illness the patient suffered a spontaneous fracture of the right femur. The child subsequently died, and at autopsy the typical changes of lymphatic leukemia were noted.

REPORT OF A CASE

E. L., a white woman aged 52, was first admitted to Kings County Hospital on Aug. 17, 1938 because of an enlarged mass in the abdomen, weakness, fever and backache. The past

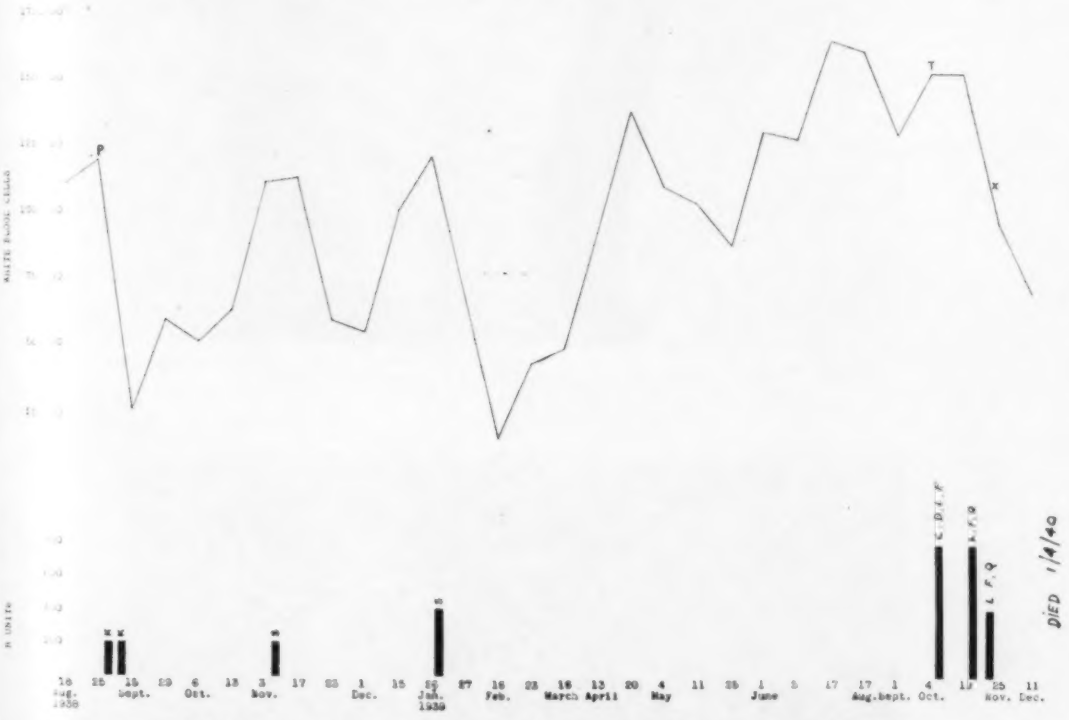


Fig. 1.—Variations in the total number of leukocytes and dosage of irradiation. At *P* skeletal roentgenograms were normal; at *T* there was pain in the right thigh, but a roentgenogram revealed no abnormality; at *X* occurred a fracture of the right femur. In the lower portion of the figure are indicated the dates, amounts and sites of irradiation: *K*, to the kidneys; *S*, to the spleen; *C*, to the cervical region of the spine; *D*, to the dorsal region of the spine; *L*, to the lumbar region of the spine; *F*, to the right femur, and *Q*, to the right forearm.

medical history was entirely noncontributory. The present illness had begun two years previously. The patient had been admitted to another hospital, where the diagnosis of chronic myelogenous leukemia was made. She received roentgen therapy there, but the data are not available. On physical examination the most significant observations were limited to the

6. Pforringer, D.: Ein Fall von Leukämie mit tumorartigen zu Spontanfrakturen führenden Markwucherungen, Fortschr. a. d. Geb. d. Röntgenstrahlen **20**:405, 1913.

7. Trusen, M.: Spontanfraktur bei einem Kinde mit lymphatischer Leukämie, Monatschr. f. Kinderh. **50**:45, 1931.

Fig. 2.—Roentgenograms of the fractured femur.

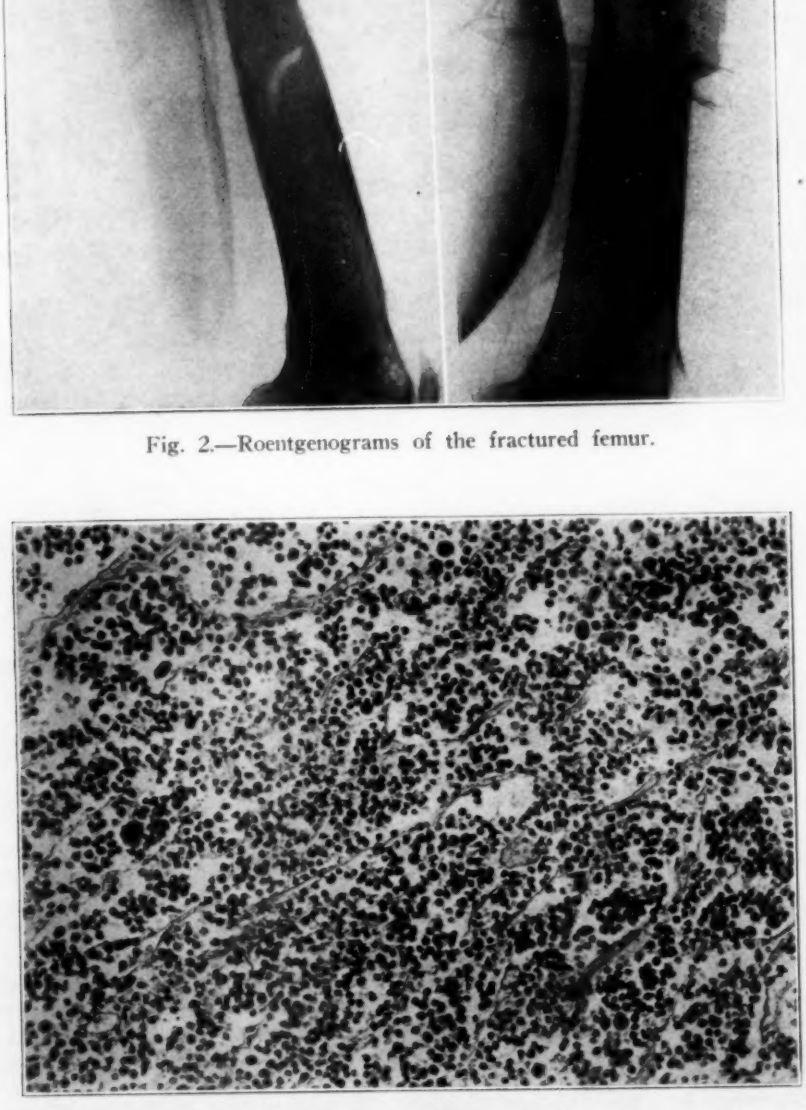


Fig. 3.—Photomicrograph of a section of a biopsy specimen taken from the site of the fracture.

abdomen. The liver was enlarged, extending 4 fingerbreadths below the costal margin; the spleen was below the umbilicus and extended to the midline. The patient appeared pale and apprehensive. No enlarged lymph nodes were felt. The blood count and all subsequent hematologic studies are presented in figure 1. Temperature, pulse rate and respiratory rate were 100.2 F., 82 and 22 respectively. The blood pressure was 108 systolic and 64 diastolic. The urea content of the blood was 38 mg. per hundred cubic centimeters, the sugar content 88 mg. and the calcium content 10.4 mg. Roentgenograms of the skeletal structures disclosed no involvement of bones. The Wassermann reaction of the blood was negative.

As shown in figure 1, the patient was treated by irradiation of the region of the kidneys, which produced a rapid fall in the number of leukocytes and improvement in her general condition. She was followed in the radiation therapy leukemia clinic. There was a gradual rise in the number of white cells, and three months later radiation to the spleen was given. A reduction of the number of white blood cells and clinical improvement were again produced. Two months later splenic irradiation was again instituted, the white cell count falling to 14,000. The patient's course followed this pattern until her admission to the hospital, on Oct. 23, 1939, three years after the onset of her illness. At this time she appeared acutely ill, and a tender, painful mass was noted on the anterior aspect of the right thigh. Ten days later, while in bed, the patient suffered a spontaneous fracture of the lower third of the right femur. Roentgenograms showed a fracture at the middle of the lower third of the femur with an area of destruction in the medullary portion of the shaft (fig. 2). The total number of white cells was then 105,000 per cubic millimeter of blood. Russell traction was applied to the injured limb. The patient's course was rapidly downhill, in spite of a gradual fall in the number of white cells. Anemia became more pronounced, and death occurred two months after the fracture. A biopsy specimen taken from the site of the fracture shortly before death showed an area of absorption of bone in which there was an infiltration of cells, mainly myeloblasts and myelocytes (fig. 3). The total duration of the illness was about three and one-half years.

SUMMARY

A case of spontaneous pathologic fracture of the femur in a patient with chronic myelogenous leukemia is presented. It emphasizes the need for repeated and complete skeletal examinations of patients with chronic leukemia. When such examinations have been carried out as a routine measure, several interesting and unexpected, as well as symptom-free, osseous lesions have been detected. When the universal distribution of the pathologic changes in the leukemic and lymphoblastomatous diseases is recognized, the occurrence of osseous lesions is not surprising. The infrequency with which they are found suggests the lack of routine and repeated roentgen examinations. The expense to the patient involved in a private hospital and the excess of routine in a municipal charity hospital are potent deterring factors.

224 Ocean Parkway.

257 New York Avenue.

286 Eastern Parkway.

ARTERIOSCLEROTIC GANGRENE

A REPORT ON REFRIGERATION PRIOR TO AMPUTATION

EDGAR R. HALEY, M.D.
BALTIMORE

The staff of a large community hospital caring predominantly for charity patients is continually faced with the problem of managing cases of gangrene of the toes and feet due to arteriosclerosis. More often than not the patient does not apply for aid until the condition is well established and he is in an advanced toxic condition, or even moribund. The problem is usually complicated by the advanced age of the patient and the frequently associated heart disease, general toxicity and diabetes. It is now generally accepted [1] that amputation of the leg is necessary if the gangrene has extended proximal to the toes. The operation often constitutes a desperate emergency for patients with far advanced toxicity, and the results in the past have been persistently discouraging. As the technic of spinal anesthesia improved, more patients withstood operation and the problem became more hopeful, but to save the life of an extremely toxic patient with advanced gangrene requiring immediate operation still constituted a difficult problem. With the publication of the work of Allen and his associates [2] on the refrigeration of gangrenous limbs new hope was held out for many patients who previously would have been lost.

While investigating tissue metabolism and local asphyxia in 1938, Allen [3] showed that a narrow elastic tourniquet about a limb causes less local damage to the tissues than a wide one. Later he [4] added chilling of the tissue to occlusion of the blood supply by the tourniquet and found that the length of life of the tissues was remarkably extended. Brooks and Duncan [5] in 1940 proved the same point by experiments on rats, finding that gangrene always develops in a rat's tail subjected to pressure of 130 mm. of mercury for eighteen hours at room temperature, whereas at 1 C. (33.8 F.) it fails to undergo gangrenous changes even after ninety-six hours of the pressure.

METHOD

For the maintenance of the cooling effect on these limbs we had a simple metal box made, long enough to hold the whole leg (figs. 1 and 2). The top is open, and a hole at one end permits entrance of the leg and thigh. A partition, which is

---

From the Peripheral Vascular Service, Baltimore City Hospitals.

1. McKittrick, L. S.: Diabetic Gangrene: Review of Nine Hundred and Seventy-Two Cases of Gangrene Associated with Diabetes Mellitus, Arch. Surg. **40**:352-363 (Feb.) 1940. Macey, H. B., and Bickel, W. H.: Amputation of the Lower Extremities in Occlusive Arterial Diseases, Surg., Gynec. & Obst. **74**:821-827 (April) 1942.

2. (*a*) Allen, F. M.: Surgical Considerations of Temperature in Ligated Limbs, Am. J. Surg. **45**:459-464 (Sept.) 1939. (*b*) Crossman, L. W.; Ruggiero, W. F.; Hurley, V., and Allen, F. M.: Reduced Temperatures in Surgery: Amputations for Peripheral Vascular Disease, Arch. Surg. **44**:139-156 (Jan.) 1942. (*c*) Allen F. M.: Experiments Concerning Ligation and Refrigeration in Relation to Local Intoxication and Infection, Surg., Gynec. & Obst. **68**:1047-1051 (June) 1939.

3. Allen, F. M.: Tourniquet and Local Asphyxia, Am. J. Surg. **41**:192-200 (Aug.) 1938.

4. Allen, F. M.: Resistance of Peripheral Tissues to Asphyxia at Various Temperatures, Surg., Gynec. & Obst. **67**:746-751 (Dec.) 1938; footnote 2 *c*.

5. Brooks, B., and Duncan, G. W.: Effects of Pressure of Tissues, Arch. Surg. **40**:696-709 (April) 1940.

movable so as to come at the level of the knee, has a smaller hole through which the leg and foot pass. Drains near the bottom remove the water as the ice melts. A heavy rubber sheet is placed over the lower half of the bed. After insertion of the patient's leg the box is placed on the rubber sheet. The patient's buttocks are supported and raised by a rubber-covered pillow. The head of the bed is raised on

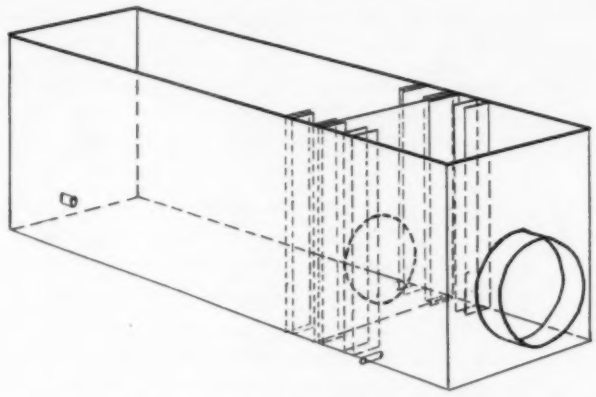


Fig. 1.—Metal box in which the limb is placed for chilling. The partition, shown in position for the average leg, is adjusted to come at the level of the knee by sliding it into the appropriate slots. Drains to which rubber tubing is attached remove water as the ice melts. All free edges of metal are rounded over wire.

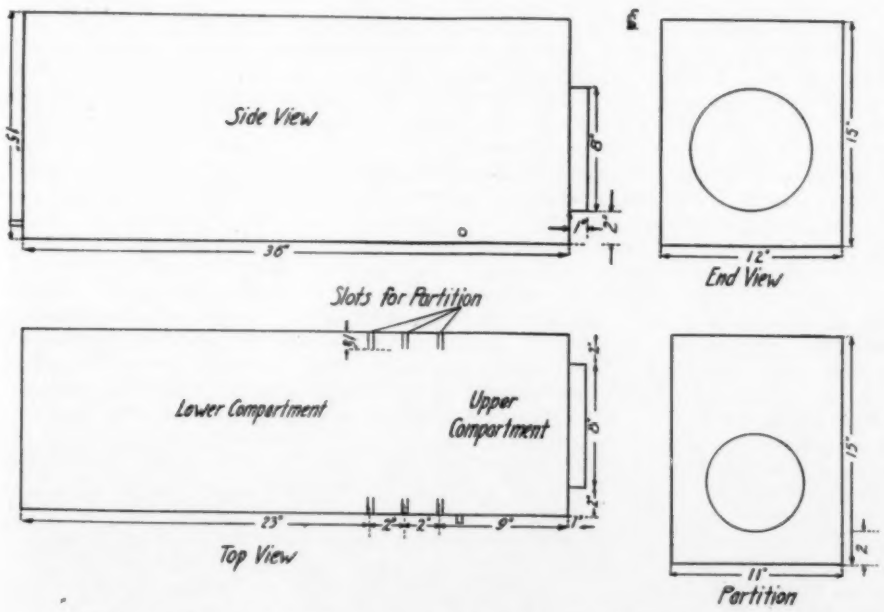


Fig. 2.—Same as figure 1, showing dimensions for construction.

6 inch (15 cm.) shock blocks, in order to keep the patient's leg well in the box and also to allow moisture which condenses on the outside of the box to drain off the foot of the bed. A small piece of rubber sheeting is cut, with a hole left which fits loosely around the patient's knee and yet blocks the hole in the partition of the box enough to prevent the ice from falling through to the upper compartment. A

second piece is fashioned for the upper part of the thigh, to block the hole in the end of the box. Finely chipped ice is now added to the lower compartment, covering the leg to the knee.

A half-hour later, when the leg is well numbed by the cold, a tourniquet of good quality gum tubing is placed about the leg at the level of the tibial tuberosity so that the ice extends 1 or 1½ inches (2.5 to 3.8 cm.) above the tourniquet. This tourniquet should be put on as tightly as possible, because the blood supply must be interrupted completely.

We have maintained this state for as long as ninety-six hours, although forty-eight hours is nearly always sufficient to bring the patient to the optimum condition for amputation. During this period general supportive measures are applied as indicated.

Six or eight hours prior to the time for operation the upper compartment is filled with ice, which should reach to the upper third of the thigh. A half-hour later a second tourniquet is tied tightly about the thigh 1 inch (2.5 cm.) below the line of chilling and yet definitely above the proposed operative field. This tourniquet must be tight enough to occlude the arterial supply unquestionably or anesthesia will not be complete. Amputation is performed between the two tourniquets, which are left in place, the anesthesia lasting for at least an hour and a half. After operation a thin dressing is applied to the stump which is then covered with bare ice bags for twenty-four hours. The patient does not have any meals deferred, preoperatively or postoperatively, and is permitted to sit up in a chair for an hour on the day of operation, after the procedure.

REPORT OF CASES

Case 1.—The first patient who received the ice-tourniquet treatment, a woman 85 years of age, was brought to the accident room at about 5 p. m. on April 23, 1942, in an extremely debilitated condition. She had at first refused to come to the hospital, and it was only after she had been irrational for three days that relatives took matters into their own hands and brought her. She was extremely restless, her son stating that she had not slept for more than an hour at a time during the previous four months because of the severe pain in her left foot. She was considerably dehydrated, having been unable to swallow fluids for twenty-four hours. The temperature was 104 F., the pulse rate 100, the respiratory rate 24 and the blood pressure 160 mm. of mercury systolic and 90 diastolic. She was not diabetic, nor did she show signs of advanced heart disease. The distal two thirds of the left foot was gangrenous, with cellulitis and edema extending halfway to the knee. Altogether she belonged to the group of patients who inevitably die unless the leg is removed and who frequently die shortly after surgical intervention. On admission treatment by the ice-tourniquet technic was instituted. One hour later she dropped quietly off to sleep and slept soundly until morning. She received 2 liters of 5 per cent dextrose in physiologic solution of sodium chloride intravenously during the night. When she awoke, about 8 a. m., she presented the picture of an elderly woman who was alert, cooperative, able to eat her breakfast by herself and in complete control of her faculties. The temperature had fallen 5 degrees during the night, and it remained normal, the highest rise being to 99 F. on the third day. The pulse rate was 80 and the respiratory rate 20. She was cheerful and extremely relieved that the pain of her foot had at last stopped. When the question of amputation arose, she flatly refused, and it was only after it had been explained that the severe pain would return if the foot were removed from the ice that she consented. From this time she became mentally depressed, stating that she wished to die.

Forty hours after her admission to the hospital the level of the chipped ice was raised to the junction of the middle and the upper third of the thigh. A second tourniquet was tied tightly at the midthigh a half hour later. After six hours she was taken to the operating room where, with the two tourniquets still in place, a supracondylar amputation was performed. No sedative nor further anesthetic was used or needed. The blood pressure at the start of operation was 170 mm. of mercury systolic and 100 diastolic, and during the operation it rose smoothly to 195 systolic and 100 diastolic. The skin was closed tightly, without drainage, after the upper tourniquet had been removed. A light dressing was applied, and

the stump was surrounded by ice bags for the next twenty-four hours. On removal of the tourniquet the compressed tissue appeared white and lifeless, but twelve hours later it was with some difficulty that the slightly erythematous mark could be identified. The tissues during the amputation were firm and cold and of excellent color, and the blood was not clotted in the vessels.

A half-hour after being returned to the ward she took her full diet and appeared as though no operation had been performed. Unfortunately the loss of the leg caused her acute depression; she did not wish to live and soon began to resist taking fluids and nourishment. The stump did well, although it drained a moderate amount of pink serous fluid for four days. The patient's depression continued and, despite all efforts, bronchopneumonia developed on the fourteenth postoperative day and she died.

The following cases are cited for comparison of the effects on the patient of spinal anesthesia induced with procaine hydrochloride and anesthesia induced with the ice-tourniquet technic.

CASES 2 and 3.—On Sept. 23, 1942, 2 remarkably similar patients arrived at the hospital, both having dry gangrene of the distal third of the right foot. Both were in good general condition, one being a white man aged 78 and the other a Negro woman aged 82. Both patients received practically the same care while in the ward prior to operation. The man, slightly younger, was definitely the stronger. His temperature stayed below 99.6 F., while the woman's ranged a full degree higher. On September 28, the woman's right leg was placed in ice to the upper thigh, and a tourniquet was applied at the level of the tibial tuberosity. An hour later a tourniquet was applied to the midthigh. She did not complain of discomfort but rather received relief from the ache of her dying foot. The following morning supracondylar amputations were performed on both patients by the same operator and team. The technic was as nearly as possible the same except that the man was given the routine medication preparatory to spinal anesthesia, ¼ grain (15 mg.) of morphine sulfate, 1/120 grain (0.5 mg.) of atropine sulfate an hour before the intraspinal administration of 60 mg. of procaine hydrochloride. He withstood the operation fairly well although he was definitely depressed.

The woman, after her regular breakfast and needing no preoperative medication whatever, underwent the same procedure. She carried on a conversation during the whole operation and was distinctly surprised to find that her leg had been removed. Within an hour of returning to the ward the woman had eaten her lunch by herself, while the man refused all food except one mouthful of potatoes, after urging. During the afternoon he appeared mildly depressed and in somewhat of a daze and was unable to sit up in a chair. He refused his supper, which meant that he had had practically no food during the day. The woman was bright, sat up in a chair for two hours during the afternoon and ate her regular supper. She needed no postoperative sedation whatever, while the man required two ⅙ grain (10 mg.) doses of morphine sulfate during the afternoon and night. The postoperative course of the stumps was almost identical. The man's stump drained moderately for one day, while the woman's drained for three days. Both stumps appeared agglutinated by the fourth day; the woman's sutures were removed on the eighth day and the man's on the eleventh day postoperatively. At the time of writing both have comfortable, firm, well healed stumps. The man's temperature rose to 101 F. on the first two postoperative days, while that of the woman was normal with one elevation to 100.2 F. on the third day.

CASE 4.—A second opportunity to compare the two anesthesias occurred at about the same time. On Aug. 20, 1942 a 66 year old white Hungarian came to the hospital complaining of pain in his right foot of four months' duration. During this time he had received pavaex treatments to both feet at another hospital. A month prior to his admission to the hospital an ulcer developed on the lateral border of the right heel, which resisted healing. The whole foot shortly became cold and bluish, and a second ulcer appeared on the dorsum. The foot was too painful to walk on and the patient was sent to the City Hospitals. Review of the family history showed that the patient's father died at the age of 58 from heart disease. His mother died at the age of 30 from an unknown cause. There was no history of diabetes in the family and no other significant findings. Before the onset of his illness the patient had been working in a bakery. He had had mild exertional dyspnea of late years.

Physical examination showed a thin white man who appeared physically older than his stated 66 years. The blood pressure was 150 systolic and 90 diastolic, the temperature 100.6 F., the pulse rate 108 and the respiratory rate 22. The skin was dry, loose and inelastic. There were scattered moist rales at the bases of both lungs. The size of the heart was within the upper limits of normal. There was advanced arteriosclerosis, and no pulse was

palpable in either foot or ankle. The right foot was cold and cyanotic, with one ulcer on the dorsum and another on the lateral aspect of the heel. The ankle showed a mild cellulitis. The urine was clear; the white blood cell count was 7,900, and the hemoglobin content was 105 per cent.

Warm saline compresses were applied to the ankle. The patient was given ¼ grain (15 mg.) of papaverine hydrochloride every four hours in an effort to increase the blood supply to the foot. He received four lumbar sympathetic blocks with procaine hydrochloride during the first ten days, during which the threatening gangrene became definite, involving the distal third of the foot. The patient's general condition was good; he was taking his meals well and was able to be up in a chair and look after himself in many ways.

On September 10 a supracondylar amputation was performed. The patient was given the routine medication of ¼ grain (15 mg.) of morphine sulfate and $\frac{1}{120}$ grain (0.5 mg.) of atropine sulfate an hour before the spinal anesthetic of 60 mg. of procaine hydrochloride was administered. The operation was the standard one that is used routinely in this hospital for supracondylar amputations. During the operation the blood pressure dropped to 95 systolic and 60 diastolic but was restored to the preoperative level with vasoconstrictors.

After the operation the patient was extremely depressed, although not particularly more so than the average elderly patient after a major operation and spinal anesthesia. His depression, however, was emphasized when he was compared with patients who had had the same procedure with the ice-tourniquet anesthesia. What little he ate for forty-eight hours was hand fed. He was not able to sit up for two days but lay in a stuporous slump. His memory of this period was of a vague horrible dream. After forty-eight hours his strength gradually returned, and he went on to an uneventful recovery, the stump being well healed when he was discharged from the hospital sixteen days later.

During his last week in the hospital the other foot showed signs of embarrassed circulation, with coldness, cyanosis and tenderness. The patient insisted on leaving despite this new involvement, but four days later, on September 30, he returned with the toes and distal third of his remaining foot in an early gangrenous condition. The area was painful and very tender. His temperature was 98 F., the pulse rate 80 and the respiratory rate 20. The general physical condition had remained unchanged since his previous admission, and the stump was well healed, firm and not tender. He was treated as before, but definite dry gangrene of the toes and distal half of the foot developed. On the evening of October 7 the left leg was placed in the box and the induction of anesthesia by the ice-tourniquet method was begun. The patient had no discomfort except a mild ache for the first ten minutes of contact with the ice. He slept well and ate a full breakfast next morning. About 10:30 a. m. he was taken to the operating room and an operation identical to the previous one was performed by the same operator on his remaining leg. Throughout the operation the patient carried on a spontaneous conversation and complained of no pain whatever. The blood pressure remained perfectly even. As the operation was being finished he mentioned that he was hungry, and within fifteen minutes after leaving the operating room he had eaten a full soft diet by himself, while sitting up in bed. Two hours later, on his own suggestion and unassisted, he got into a wheel chair and visited friends about the ward. At no time, either preoperatively or postoperatively, did he receive or need any sedation. For twenty-four hours ice caps were kept on the stump, which drained a moderate quantity of sanguinous fluid for two days. Although healing was slightly slower than after the first amputation, the stump was well healed in two weeks and was firm and in good condition.

COMMENT

The details of our management of patients with arteriosclerotic gangrene depends on the urgency of their condition. If gangrene is well established in the foot with a spreading cellulitis and the patient is in a toxic condition, he obviously will benefit from an immediate physiologic amputation. Then for forty-eight hours general supportive measures can be carried out with the patient physiologically free of the offending limb. As a second phase of the treatment actual amputation is then performed with a more reasonable expectation of a satisfactory outcome. On the other hand, if there is no infection present and the patient is in relatively good condition amputation does not constitute an emergency, and if the ice-tourniquet technic is to be used in order to minimize the general operative depression it need be applied for only a few hours prior to the time for operation.

When the limb is first chilled it aches moderately for ten or fifteen minutes, but no patient has complained more than just to mention it. In cases in which there is severe pain from the gangrene, the ice affords a definite relief. The application of the tourniquet causes moderate discomfort also, but it is in no way excessive if the leg has been well chilled. All sensation from the knee down stops entirely within a few more minutes.

In every case the temperature of patients with only gangrene and spreading cellulitis fell to normal within twelve hours of the application of the ice-tourniquet treatment. By far the most dramatic and convincing factor of this whole management was the tremendous change for the better which occurred in the first twenty-four hours. To be convinced, it is necessary to see this change, since it is difficult to evaluate statistically. Suffice it to say that the improvement described in the first case has been duplicated many times.

In the six month period since the ice-tourniquet technic was first tried for the management of arteriosclerotic gangrene 20 amputations have been performed at this hospital, 7 with spinal anesthesia (60 mg. of procaine hydrochloride), 3 with intravenous pentothal sodium anesthesia and 10 with ice-tourniquet anesthesia. From the start it was evident to all concerned that the preoperative phase of this management had unquestionable value to the debilitated, toxic patient in desperate need of supportive measures before operation. The actual value of the ice-tourniquet procedure as anesthesia for the operation appeared more open to criticism. It was suggested that the preoperative chilling be used from the knee down and that the amputation be performed above the knee, with spinal anesthesia. In this way operation could be performed without a tourniquet, better hemostasis thus being permitted; the incision would be through "live, healthy" tissue which had not been deprived of its regular blood supply and chilled considerably below body temperature for several hours, and the necessity for hurrying the operation owing to a short lived anesthesia would be relieved.

It was with the intention of properly evaluating the aforementioned criticisms that the 20 amputations were classified as to the anesthesia used. The 3 patients receiving the intravenous anesthetic had each been prepared for ice-tourniquet anesthesia. In each case the anesthesia was poor because the arterial blood supply had not been occluded by the upper tourniquet.

The second phase of treatment, namely, the use of the ice-tourniquet technic to produce anesthesia, has received critical evaluation in this hospital as to its actual worth. At first there was a tendency to believe that eventually ice-tourniquet management would be reserved as a preoperative measure for patients in a critical condition and badly in need of supportive measures prior to operation. Then, after twenty-four or forty-eight hours, with the patient in a reasonably good condition, the amputation could be performed with the patient under low spinal anesthesia. Because of this belief, spinal anesthesia was used for amputations on relatively strong patients without complications. Patients for whom the ice-tourniquet management was started as a preoperative supportive measure were carried through the amputation under ice-tourniquet anesthesia. Actually it was the nursing personnel who called attention to the fact that the patients having their legs amputated under the ice-tourniquet anesthesia were much stronger and more cooperative postoperatively. It was pointed out that when spinal anesthesia was used frail patients were profoundly depressed for thirty-six or forty-eight hours after operation, while when the ice-tourniquet technic was used they had a relatively good appetite immediately postoperatively, moved about in bed to help

themselves and were able to sit up in a chair immediately. The contrast between the immediate postoperative reactions following the two types of anesthesia was noted again and again.

The increased drainage after amputations for which ice-tourniquet anesthesia was used was noted also by Allen. His explanation was that the chilling of the stump delays agglutination and so allows the fluid to drain out of the tissues. Supporting this statement is my observation that by the end of a week there is little if any difference in the appearance of the wounds whether the operation was performed under spinal anesthesia or done with the ice-tourniquet technic. In my short series the postoperative temperature took nine days, on the average, to return to normal after spinal anesthesia, as against only four and one-half days after ice-tourniquet anesthesia. Better drainage due to chilling may well be the reason for the difference.

I believe that the use of two tourniquets is a distinct advantage. The later application of the upper tourniquet allows the tissues through which the operation is performed to be washed free of and recover from the toxins which were being absorbed from the infected foot. This advantage is lost when only one high tourniquet is used.[1]

In a recent report of a case Schiebel[6] stated that for good anesthesia the tourniquet should be "just tight enough to restrict venous return, but not tight enough to interfere with arterial inflow." It must be emphasized again that in my experience satisfactory anesthesia was secured only when the arterial flow was definitely interrupted. It is rather surprising how much force is required to occlude the blood flow entirely in arteriosclerotic limbs.

SUMMARY

The ice-tourniquet treatment has a very definite place as a preoperative measure in the management of debilitated patients with gangrene.

Operative or postoperative reactions following the use of the ice-tourniquet method for anesthesia are slight compared with those following the use of spinal anesthesia.

The need for preoperative and postoperative sedation is practically eliminated.

The stump is apparently not harmed by the ice-tourniquet treatment, and healing is perfectly satisfactory.

The management of 4 cases is presented in detail. It is suggested that the use of two tourniquets with amputation between them, constitutes an improvement over the use of one tourniquet.

225 Santa Monica Boulevard, Santa Monica, Calif.

6. Schiebel, H. M.: Use and Evaluation of Anesthesia by "Freezing" for Surgery of Extremities in Diabetic Patients: Case Report, North Carolina M. J. **3**:227-229 (May) 1942.

NERVE REGENERATION IN THE RAT FOLLOWING TUBULAR SPLICING OF SEVERED NERVES

PAUL WEISS, PH.D.
CHICAGO

For many years a method for uniting severed nerves has been used in experiments in my laboratory which has proved so superior to the conventional suture methods that the possibility of adapting it to the surgical needs of human beings deserves serious consideration. While the studies pursued with this method have branched into many phases of the problem of nerve restoration, the following brief account will confine itself to those aspects which seem to be of immediate practical interest.

The method consists in splicing the stumps of a severed nerve by inserting them in a closely fitting sleeve of live artery. First devised for use in the frog and toad [1] the method was then applied to the rat [2] and has lately been used extensively in work on this animal. Save for a brief note,[3] no special description of the technic and of the processes of nerve regeneration following its use has as yet been given. This missing information will be supplied in the present paper.

It should be understood from the outset that the purpose of using an arterial link to reunite ends of a nerve is primarily to provide a firm tie between the stumps of a sort that will favor regeneration of nerve fibers and prevent formation of scar tissue. It is not intended as a means of bridging larger gaps in a nerve by providing regenerating fibers with a pipeline, as it were, for which purpose "tubulation" or "tubularization" of nerve stumps has been used, with varying success, in the past.[4] As nerve ends can never be strictly apposed in the microscopic sense and, in fact, for best histologic results never should be,[5] the function of the arterial tube as a guide for nerve fibers will also come up for consideration, but this is a secondary matter. The main purpose of use of the arterial sheath is to eliminate the need of suturing the stumps together, so that the various hazards to nerve regeneration inherent in ordinary methods of suturing may be avoided. Owing to the greater tensile strength of the arterial link as well as to some other advantages to be discussed in subsequent paragraphs, tube splicing seems to be

From the Department of Zoology, The University of Chicago.

This research was done under a government contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Chicago. It was aided by the Dr. Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago.

1. Weiss, P.: Selectivity Controlling the Central-Peripheral Relations in the Nervous System, Biol. Rev. **11**:494-531, 1936.

2. (*a*) Sperry, R. W.: The Effect of Crossing Nerves to Antagonistic Muscles in the Hind Limb of the Rat, J. Comp. Neurol. **75**:1-19, 1941; (*b*) Transplantation of Motor Nerves and Muscles in the Forelimb of the Rat, ibid. **76**:283-321, 1942. (*c*) Weiss and Campbell: Unpublished data.

3. Weiss, P.: Re-Union of Stumps of Small Nerves by Tubulation Instead of Suture, Science **93**:67-68, 1941.

4. Stookey, B. P.: Surgical and Mechanical Treatment of Peripheral Nerves, Philadelphia, W. B. Saunders Company, 1922. Pollock, L. J., and Davis, L.: Peripheral Nerve Injuries, New York, Paul B. Hoeber, Inc., 1933.

5. Nageotte, J.: L'organisation de la matière dans ses rapports avec la vie, Paris, F. Alcan, 1922.

superior, on the whole, to the only other sutureless technic of nerve union, the blood plasma technic of Young and Medawar.[6] However, there will be situations in which arterial splicing is not practicable while plasma suture is.

The adequacy of the arterial link has been proved both with regard to its mechanical function of tying and holding the nerve ends together and with regard to its capacity to provide most favorable conditions for the outgrowth of regenerating fibers from the proximal stump and the invasion of the peripheral stump. The main advantages are as follows:

1. Clotting blood plasma and tissue fluid seal the arterial sleeve tightly to the surfaces of the inserted nerve ends. As adhesion is proportional to the size of the adhering surfaces, the tensile strength of an arterial juncture, with the outer wall of the nerve and the inner wall of the artery in extensive contact, is naturally much greater than that of end to end blood plasma fusion, as practiced by Young,[7] just as two threads glued lengthwise to a common third thread are more firmly united than if they were merely joined end to end.

2. The arterial link permits, without loss of holding strength, leaving a slight gap between the nerve ends, which seems to be beneficial to smooth nerve regeneration.

3. The introduction into the nerve of a foreign body, such as catgut, silk or nylon, is avoided. This not only precludes the foreign body reactions common in such cases but, more significantly, eliminates the disorientation effects which suture threads exert on the regenerating nerve fibers in their vicinity.

4. Longitudinal stresses, which would otherwise be taken up by the unelastic suture threads, are transmitted through the tissue matrix filling the gap between the two cut ends and force that matrix into longitudinal orientation, which, in turn, imparts corresponding orientation to the regenerating nerve sprouts.

5. As a corollary of the preceding statement, the disorientation commonly observed in the so-called scar region is prevented, which reduces the incidence of fiber branching and of formation of local neuromas to insignificant proportions.

6. The uninterrupted canalization between the two nerve stumps prevents both the escape of bundles of nerve fibers into the surrounding tissues and the ingrowth of scarifying fibrous tissue into the wound.

7. Branching and diffusion of fibers at the suture level thus being avoided, conditions are more favorable for an orderly point to point reconnection between central cells and peripheral organs than is common in nerve regeneration. This, in turn, must be expected to have important bearings on functional restoration. Instead of allowing fiber branches to scatter widely all over the peripheral stump, the arterial sleeve insures the preservation of some degree of topographic localization throughout the process of regeneration.

8. Arterial splicing makes it possible to mend small nerves for which ordinary suturing would not be feasible.

In support of these statements, I shall present the results of a thorough histologic study of 23 sciatic nerves of rats spliced with arterial segments, 10 of which were studied in regularly spaced cross sections while 13 were studied in serial longitudinal sections. On 8 of the transversally cut nerves complete fiber counts through representative regions, old and regenerated, were made. Moreover, most

6. Young, J. Z., and Medawar, P. B.: Fibrin Suture of Peripheral Nerves, Lancet **2**:126-128, 1940.

7. Young, J. Z.: The Functional Repair of Nervous Tissue, Physiol. Rev. **22**:318-374, 1942.

animals before being killed were subjected to physiologic tests in which the isometric tension produced by the gastrocnemius muscle on stimulation of the regenerated sciatic nerve was recorded.

TECHNIC

While many kinds and sizes of nerves have been used, the following description will be confined to the suture of the sciatic nerve in rats of between 200 and 300 Gm. body weight. Arteries of proper diameter are furnished by the trunk aortas of smaller animals and the carotid and femoral arteries of larger animals. The artery which appears in all figures 1 *B* to 7 of this report is a segment of aorta.

The sciatic nerve is severed in the proximal part of the thigh, either at the level where it is still uniform or at a more distal level, where it is already internally subdivided into a peroneal and a tibial branch. After transection the two ends of the nerve are inserted into an arterial sleeve previously prepared in the following way. A segment of artery about 1 cm. in length is transferred into Ringer's solution, where it is freed from its blood content by gentle squeezing. A specially designed splicing forceps is then introduced into the empty lumen. The procedure is illustrated in figure 1 *A*. The splicing instrument consists of a forceps terminating in two half-cylinders, which when closed form a tube. Into this fits a solid core of conic shape (fig. 1 *A,a*). For use on smaller nerves the half-cylinders are fashioned by grinding down hypodermic needles of suitable gage. These are then soldered to the prongs of a steel forceps. For greater rigidity the proximal part of the needle is filled with solder. Both halves are so adjusted that when the forceps is closed they will meet edge to edge. Since the base of the conic core has the same diameter as the outside of the tube, the closed forceps and the inserted core form a continuous tapering rod. In this position the instrument is introduced into the artery, as shown in figure 1 *A, b*. From the tapering core the arterial fragment is then pulled over the cylindric end of the closed forceps, whereupon the core is withdrawn and the forceps slightly opened so as to distend the artery (fig. 1 *A, c*). Since in the case of thick-walled arteries the spring of the forceps may not be sufficient to produce distention, it is advisable to fasten a setscrew between the two prongs of the forceps, the turning of which can force the branches apart. The open forceps is then slipped over one of the nerve stumps so that the cut end will come to lie between the two prongs inside the widened orifice of the arterial sleeve. After the nerve end is clutched by closing the forceps, the arterial fragment is pulled back from the forceps over the nerve, as shown in figure 1 *A, d*. When the forceps is withdrawn, about one half of the length of the sleeve is left over the nerve end while the other half is empty (fig. 1 *A, e*).

To introduce the other nerve end into this empty part, an instrument illustrated in figure 1 *A, f* and called the "spreader" is used. It consists of a clip fashioned from an elastic wire band and acting like a forceps with reversed tips. When this clip is closed by lateral pressure with a needle holder, the two free end pieces are brought in apposition and can then be easily inserted into the open end of the artery. On release, the spring of the instrument opens the artery, as shown in figure 1 *A, g*. By appropriate bending of its apex, the elasticity of the instrument can be adjusted so as to distend the artery to just the desired amount. The nerve stump is then introduced into the opening and pushed on until it meets the previously inserted stump. When the spreader is withdrawn, the released artery by its elasticity clamps down on the second nerve stump. The surfaces of the spreader must be polished, for rough edges tend to pull the nerve out again. The grip of the arterial sleeve on the two nerve ends is then tightened by stretching the artery lengthwise with two pairs of forceps. This secondary elongation entails

a slight separation of the formerly closely apposed cut surfaces, as is shown in figure 1 *A, h*. However, such a small gap, measuring in length not more than the diameter of the nerve, is not detrimental but apparently even favorable to smooth crossing of the regenerating fibers from the proximal into the peripheral stump.

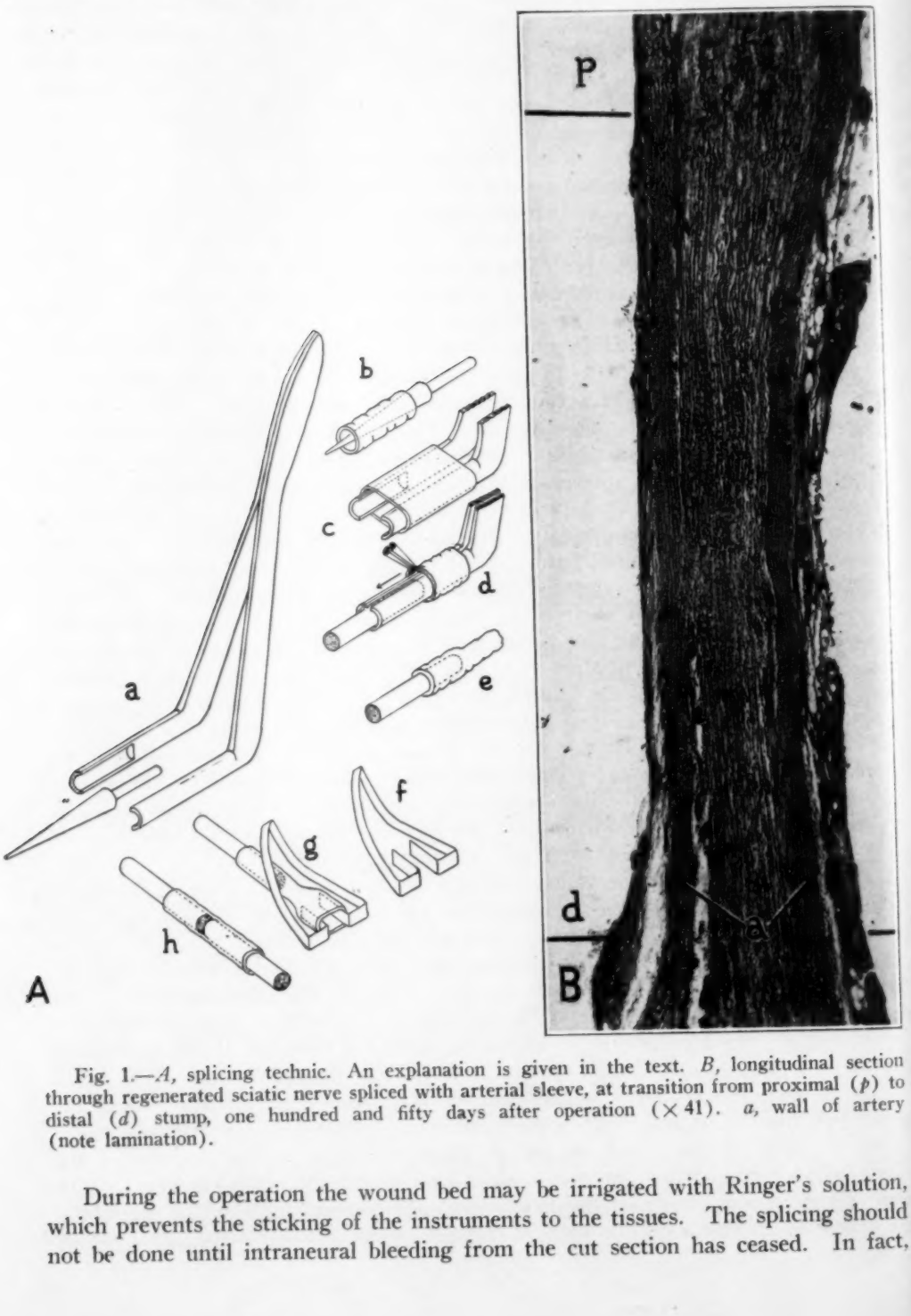


Fig. 1.—*A*, splicing technic. An explanation is given in the text. *B*, longitudinal section through regenerated sciatic nerve spliced with arterial sleeve, at transition from proximal (*p*) to distal (*d*) stump, one hundred and fifty days after operation (× 41). *a*, wall of artery (note lamination).

During the operation the wound bed may be irrigated with Ringer's solution, which prevents the sticking of the instruments to the tissues. The splicing should not be done until intraneural bleeding from the cut section has ceased. In fact,

if there should be secondary bleeding into the gap between the two stumps after the splicing, it is indicated to withdraw the peripheral stump from the sleeve again, remove the blood clot and resplice. The effects of plasma clots left between the stumps are being further investigated and will be reported in a later communication.

After the splicing, all excess fluid is blotted or sponged from the surroundings. Leaving the exposed area to dry for several minutes results in a firm tie between the wall of the artery and the inserted nerve stumps. Residues of blood plasma along the inner wall of the artery obviously help in cementing the union. That this is not absolutely essential for successful splicing, however, is demonstrated by the fact that arteries kept in Ringer's solution on ice for one or two days are quite adequate, although their inside is much more slippery than that of fresh artery. When these are used, the clotting of the fresh tissue juice along the sticky surface of the nerve obviously provides the sole cementing agent. The wound may then be closed. Experiments with prolonged exposure show that after fifteen minutes the tie has become firm enough to withstand moderate tension. Pending more exact determinations of the tensile strength of arterial joints at various intervals after the operation, it may be stated that in some test experiments in which the wound was opened a few hours after the operation noticeable pull was required in order to break the link between the two nerve stumps. Since the adhesive power between arterial wall and nerve surface is proportional to the extent of surfaces in contact, and hence to the length of the arterial sleeve, the latter will have to be made the longer the more tension the spliced nerve is expected to sustain.

HISTOLOGIC OBSERVATIONS

A number of typical examples may serve to illustrate the type of nerve regeneration obtained with arterial splicing. Fixation in Bouin's fluid under stretch and impregnation with silver salts according to the method of Bodian, sometimes supplemented by staining with Mallory-azan stain, have been used throughout.

Figure 1 *B* presents a longitudinal section through the region of a splice one hundred and fifty days after the operation. The proximodistal direction is indicated in the picture. The central mass of nerve fibers can be seen to be bounded on either side by the laminated arterial wall. The seven to eight layers of elastic tissue forming this wall can be clearly recognized. The levels of the original cut surfaces can be reconstructed from the extent of the original epineurium of the nerve stumps. Since the perineurium and epineurium have failed to regenerate, their margins indicate approximately the farthest extent of old nerve. These levels are marked in the figure by solid lines. Between them the nerve fiber masses are devoid of epineurium and sheathed directly by the arterial sleeve. This region then corresponds roughly to the former gap. Since there may have been some slight retraction of the epineurium on either side of the gap, the original distance between the nerve ends may not have been quite as large as it would seem from the final picture. At any rate, this is the region which corresponds to the so-called scar region, or suture line, of a nerve sutured by ordinary methods. It can be seen from the picture that in this area the nerve is attenuated. This is due in part to the absence of the epineurium and in some measure to the smaller size of the nerve fibers. As will be shown later, however, it does not express a significant decrease in the number of fibers.

Several striking features of the regenerated nerve become obvious at once. The nerve fibers run in a straight course and in parallel orientation from the

proximal stump into the gap region, continue without deflection or confusion through this region and pass on straight into the peripheral stump. Nowhere is there evidence of the profuse branching, straying about and intermingling of fibers commonly observed at the transition from the proximal to the peripheral stump of nerves sutured by ordinary methods.

Figure 2 gives an enlarged view of the transition from the gap region into the peripheral stump of the same nerve as in figure 1 *B*. The entrance into the old peripheral stump is marked by the appearance on one side of the picture of the old epineurium; on the other side some fat tissue has penetrated. The central part of the picture is taken up by the strands of regenerated nerve fibers. These form a compact mass, packed about as densely as they are in normal nerve. They

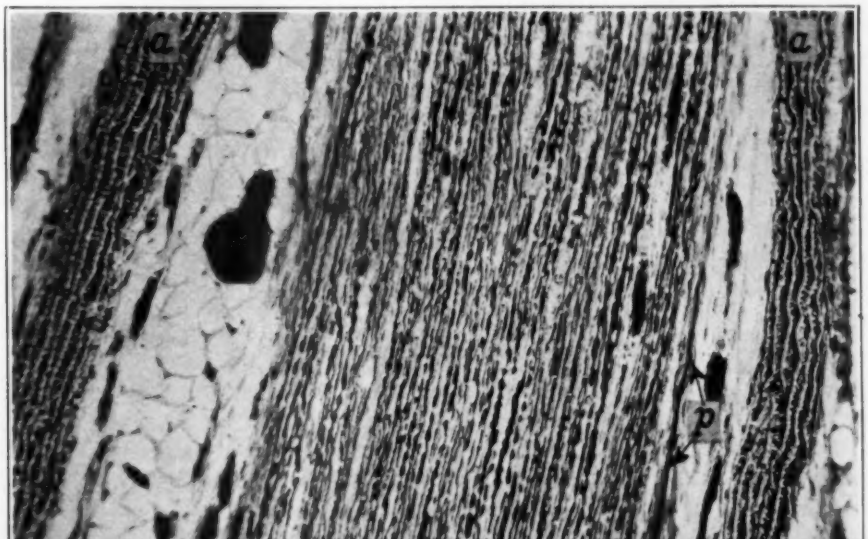


Fig. 2.—Same preparation as in figure 1 *B* at transition from "gap" to peripheral stump (× 115); *a*, arterial wall; *p*, perineurium.

follow a well oriented straight course. Their size varies from very thin to relatively large fibers. In estimating size of fibers it must be remembered that with the methods of fixation and impregnation used in these studies large axis-cylinders collapse in many places along their course, which gives them the appearance of a string of beads, each myelin segment showing several constrictions. A further discussion of size of fibers will be presented later.

To either side of the nerve mass one sees spaces filled partly with vascularized fat tissue and partly with loose connective tissue, the extent of the latter being exaggerated by shrinkage during fixation. These layers separate the nerve core from the wall of the artery, which can be recognized by the characteristic lamination of the elastic tissue. Lack of intimate contact between the nerve fibers and the

inner wall of the artery is a frequent occurrence near the original arterial openings, where the epineurium and adhering loose connective tissue were tucked into the artery. In many spliced nerves, of which the present one is a typical example, there has been a definite tendency of this tissue to become converted into fat tissue, which then has remained interposed between the arterial wall and the surface of the nerve. Whether the breakdown of myelin with the liberation of phospholipids in this region has anything to do with this transformation into fatty tissue remains a matter for speculation. At any rate, this process remains localized about the ends of the sleeve, while in the intermediate zone close contact between the nerve fibers and their arterial container is preserved. This is further illustrated by the study of cross sections.

Figure 3 shows cross sections through a spliced and regenerated sciatic nerve one hundred and eighty-one days after operation at five different levels. The location of these levels is indicated in the accompanying diagram (fig. 3 *F*). The nerve had been transected at a level distal to its bifurcation into the tibial and peroneal divisions. Section *A*, through the proximal stump near the proximal end of the arterial sleeve, shows the two nerves with their perineuriums, surrounded by the artery. Some fat tissue can be seen wedged between the old epineurium and the arterial wall. This level is still more than 2 mm. proximal to the original level of transection. Yet the tibial nerve (lower left) gives evidence of being composed largely of regenerated fibers. In contrast, the peroneal division (upper right) shows essentially the organization of normal nerve, although it, too, contains a certain contingent of regenerated fibers. The situation is explained by the fact that ascending traumatic degeneration following transection of a nerve may extend several millimeters centrad from the wound, so that regeneration actually starts from a level slightly proximal to the actual level of sectioning. The difference between the peroneal and the tibial nerves in this case is simply due to the fact that after transection the latter has retracted a little farther in its sheath (fig. 3 *F*). Section *B*, which lies 2.5 mm. distal to *A*, shows the end of the proximal stump of the peroneal nerve, while the fibers of the tibial nerve at this level have already entered the gap between the original stumps. Consequently, the peroneal nerve (in the center) is still surrounded by some of its perineurium, while the fiber masses emerging from the tibial nerve (on the left) are applied directly to the inner wall of the artery. Section *C*, which is 2 mm. distal to section *B*, lies entirely within the gap region, and here the fiber bundles fill the lumen of the artery completely, except for a small extension of vascularized fat tissue on the right.

This is, then, the aspect in cross section of the fiber masses between their emergence from the original proximal stump and their entrance into the original distal stump; in other words, the suture line corresponding to the scar region of ordinary nerve sutures. The fibers can be seen arranged in small bundles, typical of regenerated nerve, with some larger spaces in between. It will be noted that nearly all fibers appear hit in their cross section and that practically none course in the plane of sectioning. This is merely another expression of the straight, parallel, longitudinal orientation of the regenerated fibers. Section *D*, 2.5 mm. distal to *C*, is from the region of the old peripheral stump of the tibial and peroneal nerves, still inside the arterial sleeve. Both nerves are completely refilled with nerve fibers, surrounded by their old perineurium and again accompanied by fat tissue, as previously discussed. Section *E* introduces a still farther distal level, 10 mm. from *D*, where each nerve has become subdivided into branches. Except for a few blank spaces, these branches have received their full complement of nerve fibers, and, as can be seen, many of these fibers have assumed fairly large diameters.

Figure 4, finally, gives details at higher magnification from sections 3 *A*, *C* and *D*, respectively. Except for an occasional straggler coursing obliquely or transversally, the vast majority of fibers can be seen to be oriented perpendicular to

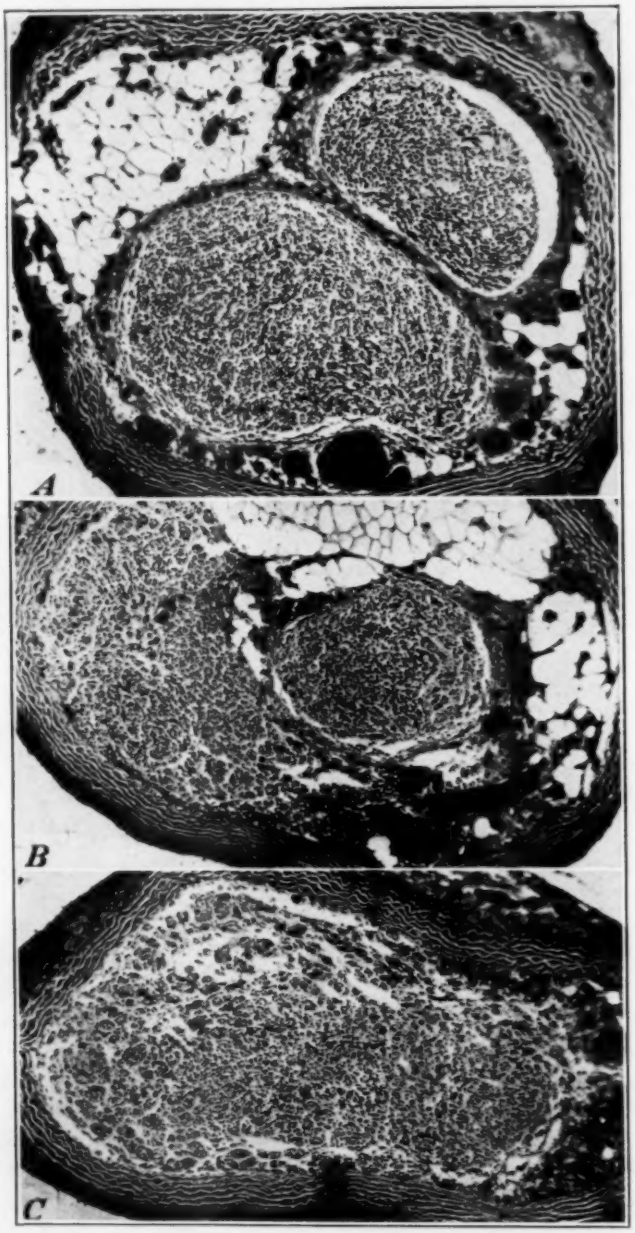


Fig. 3.—Cross sections through an artery-spliced and regenerated sciatic nerve one hundred and eighty-one days after the operation. Further explanation is found in the text (× 62).

the plane of sectioning, i. e., parallel to the axis of the nerve. A comparison of the middle section, which runs through the gap region of the nerve splice, with the other two sections reveals that on the whole the reorganization of the nerve is somewhat further advanced inside the old stumps, both central and peripheral,

than it is in the intervening zone. In the latter the fibers are more loosely packed, there is a somewhat greater proportion of endoneural tissue and there seem to be fewer fibers of the largest caliber. It would seem, therefore, that in the peripheral stump, where the fibers had the benefit of traveling inside the old

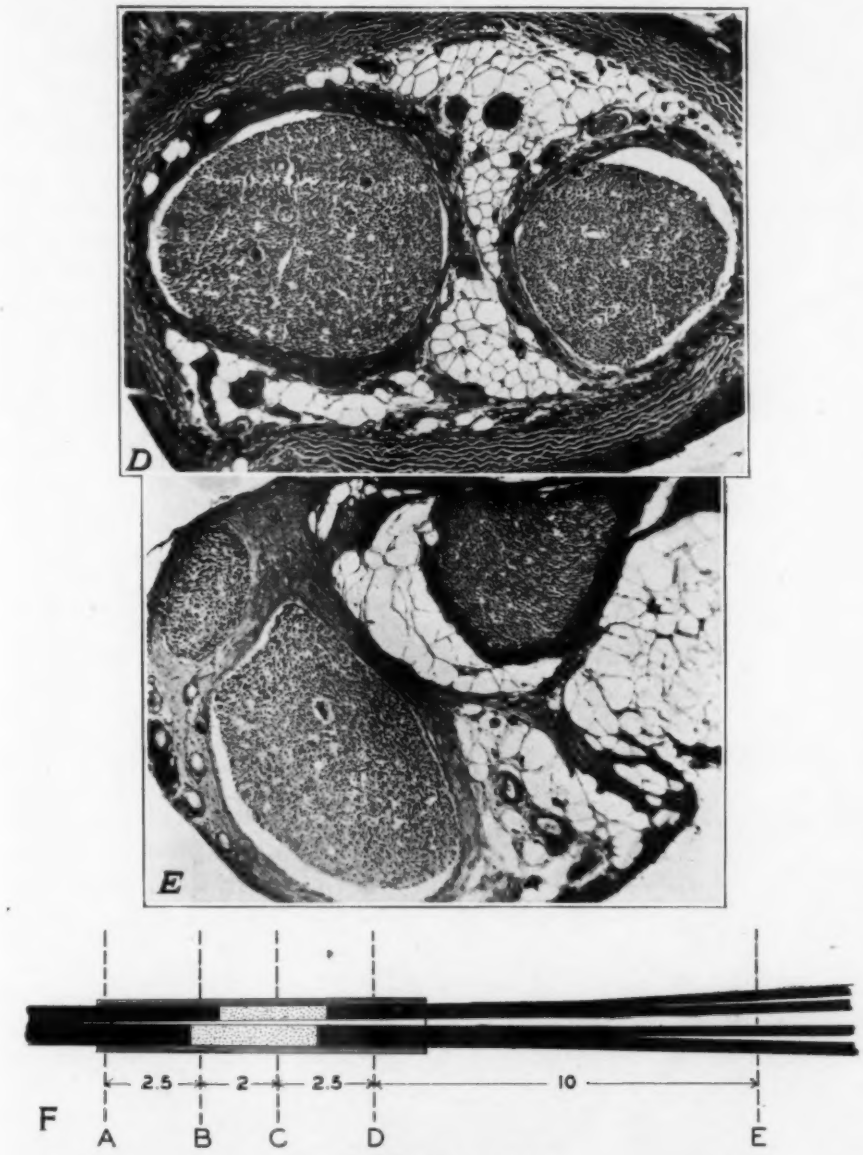


Fig. 3.—(Continued).

degenerated Schwann sheaths, reorganization and maturation took place at a slightly faster rate than in the pathless area of the gap. Sections from other spliced nerves confirm this impression. However, it will require more intimate studies to determine whether the observed differences are significant.

With regard to size of fibers, a striking difference exists between the old fibers in the proximal stump and their regenerated peripheral parts, as seen in figure 3 *B*

and *C*. The left upper half of figure 3 *A* shows a sector of the original fiber complement of the peroneal nerve. While many of these fibers were hit slightly obliquely and therefore appear somewhat larger, most of them, particularly toward

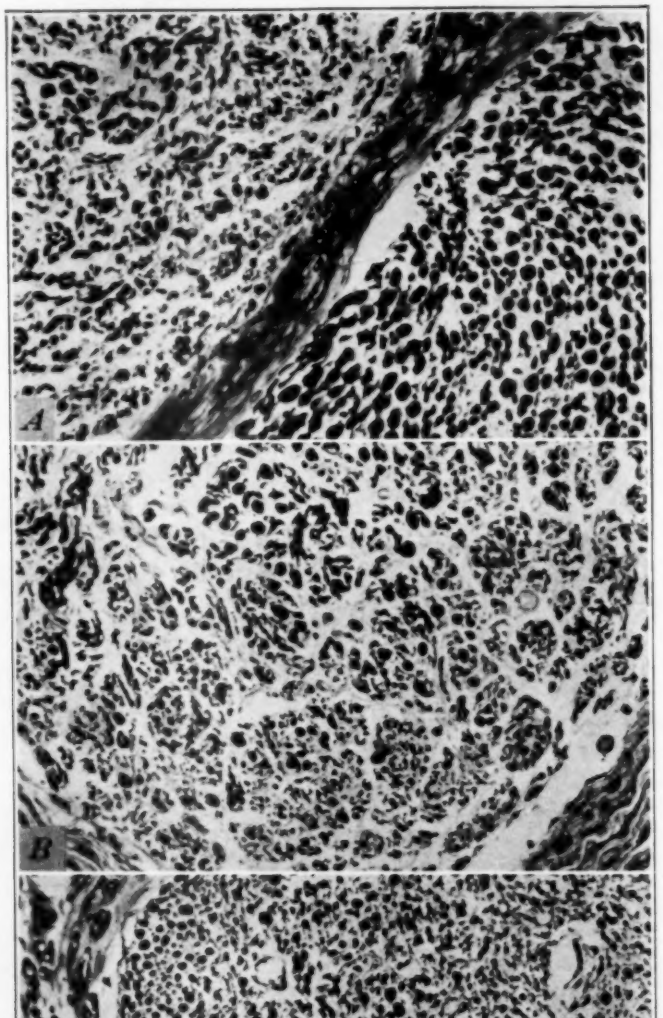


Fig. 4.—Details from cross sections *A*, *C* and *D* of figure 4 (× 210).

the center of the nerve, appear in straight cross section. As one can readily see, the proportion of large diameter fibers in this old nerve is much greater than is to be found at any one of the more distal levels. It is well known that the newly

regenerated branches, growing out from a severed central stump, are all very thin fibers of more or less equal diameter. It is only secondarily that the peripheral parts of some of the regenerated fibers will grow in thickness, tending toward the restoration of the differentials of fiber size existing in normal nerves. How closely the original pattern of size distribution is restored and to what extent the resumption of a definite caliber is controlled by the origin of the fiber branch, the path it has taken, the length it has attained and the termination it has reached have not yet been systematically investigated, although some occasional attention has been given to the problem. However this may be, it is obvious that in the present nerve the fiber composition of the peripheral trunk has not yet been fully restored to its original condition in six months after the transection. By far too many fibers are still in the small and very small classes, with fibers of the larger caliber comparatively scarce.

All other nerves studied on which the operation was performed properly conform to the type of regeneration just described. In all of them the nerve fibers have retained their straight longitudinal course throughout the gap and peripheral stump. Occasionally single fibers or small bundles do run off at an angle for short distances, but these occurrences seem to be negligible when contrasted with the strict longitudinal orientation of the bulk of the fibers. Perineurium and epineurium have not regenerated, and within the stretch intervening between the original cut levels the fibers are in direct contact with the inner surface of the arterial sleeve, which within this area, then, serves as nerve sheath.

The vascular supply of the regenerated nerves is partly intraneural, with most vessels running lengthwise inside the nerve, and partly perineural, with accessory vessels from the interstitial fat tissue entering the nerve.

FIBER COUNTS

Counts were made of the number of nerve fibers seen in cross sections of 8 of the nerves operated on.[8] Data for 5 of these, for which complete counts are available through all three critical levels, i. e., through proximal stump, gap and distal stump, are included in the following tabulation. The remaining 3 counts are incomplete in that no enumeration was made at the level of the gap, and these are therefore omitted.

The counts were made according to the method regularly used in this laboratory in the past.[9] The margin of error of this method was found in earlier observations to lie below 2 per cent for fibers stained for myelin [10] and within 6 per cent for silver-impregnated fibers.[9] In view of the large number of very fine fibers present in newly regenerated nerve, increasing the difficulty of identification, the counting error may be considered higher in the present tabulations. The results are summarized in the table.

The most striking point is the close correspondence between the number of fiber sections counted in the old proximal stump of the sciatic nerve and the number of regenerated fiber sections within the gap area. Only in nerve *B* does the gap show a deficit of nearly 20 per cent, and this is readily explained by the fact that in this experiment the artery had in one place sustained a break, through which

8. Dr. Raymond Litwiller assisted in making the fiber counts.

9. Litwiller, R.: Quantitative Studies on Nerve Regeneration in Amphibia: I. Factors Controlling Nerve Regeneration in Adult Limbs, J. Comp. Neurol. **69**:427-447, 1938.

10. Weiss, P.: Further Experimental Investigations on the Phenomenon of Homologous Response in Transplanted Amphibian Limbs: II. Nerve Regeneration and the Innervation of the Transplanted Limbs, J. Comp. Neurol. **66**:481-535, 1937.

a mass of fibers escaped into the surroundings so as to be lost for the count. In all other instances the difference between the two levels lies within the limits of the error inherent in the method. These figures, therefore, bear out completely the evidence of the histologic observations, according to which, on the whole, each fiber of the proximal stump has during its regenerative outgrowth remained single, without bifurcation. The fiber counts inside the distal stump show a distinct drop below those of the gap, varying with the distance at which the count was taken. This drop can be accounted for by the branching off from the main nerve trunks of some small fiber bundles which were omitted in the distal counts. That the decline is not necessarily an expression of incomplete regeneration is demonstrated by the fact that even in the youngest splice (*A*), studied seventy-four days after the operation, the distal stump has become fully repleted.

FUNCTIONAL OBSERVATIONS

While the relation between morphologic regeneration and functional recovery will be more fully discussed in a subsequent paper, a few remarks on the subject seem in place. Obviously the stage has been passed when one can acquiesce in

Results of Fiber Counts

Nerve	Days After Operation	Number of Fibers: Proximal Stump	Number of Fibers: "Gap"	Number of Fibers: Distal Stump	Length of Gap, Mm.
A	74	5,415	5,240	5,210	3.5
B	137	5,235	4,245*	3,218	4.5
C	143	4,435	4,855	4,075	Undetermined
D	153	4,613	4,770	3,425	2.0
E	172	5,590	5,545	4,695	Undetermined

* Break in arterial wall with extensive escape of fibers.

such general statements as that function has become "improved" or "partially restored" or has remained "abnormal." Neither sensory nor motor functions are in themselves entities; they are complex phenomena in which each phase is differentially affected by denervation and nerve regeneration. For each phase definite criteria must be established, and functional restoration must then be described in terms of these criteria. On the motor side restoration of trophic influences, electric excitability, transmissibility at the myoneural junction, reflex action, muscular power and, finally, coordination must be given separate consideration in relation to nerve regeneration. As for the restoration of muscle power, an adequate test consists of determining the maximum tension which the reinnervated muscle can produce on direct stimulation as well as on indirect stimulation through its nerve. Registered isometrically, the tension developed after direct stimulation of the muscle is a measure of the amount of functionally adequate contractile tissue, while isometric tension developed in the muscle after electric stimulation of its nerve with supramaximal shocks gives a measure of the fraction of total contractile tissue which has become reinnervated.

In the experiments with the best results, the maximal tension obtained from a gastrocnemius muscle reinnervated from a spliced sciatic nerve was approximately equal to that recorded from the opposite gastrocnemius muscle, with undisturbed

innervation.[11] This means that the muscle on the side operated on either had suffered only a minor denervation atrophy or else had become restored to its original size after reinnervation. In such instances, tensions developed after supramaximal stimulation of the nerves were likewise nearly symmetric on the two sides, proving that all of the muscle fibers in contractile condition had received reinnervation. This condition was found as early as ten weeks after splicing. This is remarkable, inasmuch as histologic preparations of these nerves reveal that most of the regenerated fibers are still rather immature, i. e., of small diameter with myelination in its early stages. In other words, the power developed by a motor unit does not depend on the state, size and degree of maturity of the efferent neuron provided neuromuscular transmission is established at all. This, of course, merely expresses the all or none nature of the contraction of muscle elements activated by nerve excitation.

In several instances, however, in which the histologic picture of the sciatic nerve as well as the fiber counts proved that the neurotization of the peripheral stump was fairly complete, the muscle power on the side of the operation, nevertheless, remained definitely deficient. Inasmuch as in most of these instances a comparison of tensions developed after direct and indirect stimulation showed that no major part of the muscle had failed to receive innervation, the weakness must be ascribed to permanent atrophy rather than to incomplete reinnervation. Such atrophy is usually evident to gross inspection, and quantitative determinations have not as yet been made. In the case of nerve B of the table, for instance, in which in spite of a sizable escape of fibers, a good two thirds of the original fiber complement of the proximal sciatic stump was found present in the distal branches at the knee, the gastrocnemius muscle was able to produce only between 10 and 20 per cent of the tension of the opposite, normal, muscle. Why the atrophy goes further in some instances than in others has not yet been determined. It is obvious that the atrophic condition of the muscles does not reflect on the number of fibers regenerated inside of the nerve stump but merely limits the number of terminal branches that will be produced inside the muscle. It is the average size, rather than the average number, of motor units that is reduced in such cases.

Return of muscle power was not paralleled, however, by return of coordinated function. While the return of sensitivity progressed gradually, as evidenced by the increasing reactions of the animals to nociceptive stimuli, motility of the legs remained inadequate. Motor responses consisted of generalized contractions of the several muscles of the leg, rather than of coordinated movements with muscles in orderly well timed operation. In general, the limbs after reinnervation behaved much as those described by Sperry [2a] after crossing peroneal and tibial nerves. Reciprocal contraction of antagonists is absent, and most responses are characterized by the prevalence of rigid plantar flexion. Sperry ascribed this incoordination to the fact that not all muscles innervated by either the peroneal or the tibial division normally operate in phase. Therefore, random redistribution of the nerve fibers of both nerves during regeneration must result in simultaneous contraction of muscles which originally were engaged independently. Since the rat is definitely incapable of any reeducation of its motor apparatus which might serve

11. The use of the side not operated on as control is somewhat objectionable, since Tamaki (Tamaki, K.: Further Studies on the Effect of Section of One Peroneal Nerve of the Albino Rat on the Intact Nerve of the Opposite Side, J. Comp. Neurol. **64**:437, 1936) has shown that unilateral transection of the peroneal nerve in the rat depresses the growth of the peroneal nerve of the opposite intact side. Allowance must therefore be made for the fact that the "control" nerve is itself slightly reduced. Whether the muscle suffers correspondingly has never been determined.

to correct inadequacies produced by nerve crossing or other irregularities of the peripheral nerve distribution,[2a, b] no improvement in the incoordinated condition of the motor responses was to be expected.

A similar explanation may be advanced for the lack of coordination in the present experiments, assuming that a large proportion of the regenerated nerve fibers have come to terminate on muscles other than the ones with which they had originally been connected. This disarrangement of central-peripheral connections was not precluded by the fact that, as one can see from the histologic studies, the regenerating fibers have essentially retained their mutual topographic relations while traversing the scar and passing on into the peripheral stump. For any degree of rotation of the peripheral stump in regard to the proximal stump in the act of splicing must have produced a corresponding distortion of the pattern of peripheral nerve distribution relative to the original pattern and thereby entailed the functional confusion of which the observed incoordinated activity was an expression. In man, in whom the well marked fascicular topography of the nerve furnishes better landmarks for the orientation of the stumps than is available in the nonfasciculated nerves of the rat, a more congruous opposition of nerve sections, such as was advocated, for instance, by Stoffel (Vulpius and Stoffel[12]), would be easier to achieve. It should be remembered, however, that many neurosurgeons do not believe such careful matching of the nerve surfaces to be necessary and that actually in man reeducation, in the sense of a reorganization of the central impulse patterns, might remedy the inadequacies resulting from altered peripheral connections, for which the rat, as has already been stated, has no remedy.

FAILURES

While the arterial splice when properly performed creates the most favorable conditions for smooth and unimpeded nerve regeneration, improper handling of the method may lead to failures just as severe as though no union of the stumps had been attempted. It has been well known since the work of Cajal[13] that even when the stumps of a severed nerve are left separated a trickle of nerve fibers from the proximal stump will finally find its way into the peripheral stump. The mechanism of this reunion, originally postulated to be chemotropic, was suggested by Dustin[14] to be haptotropic, and recent experiments[15] have furnished evidence that it is really a matter of contact guidance, rather than of attraction over a distance. Those nerve fibers which happen to strike on a peripheral degenerated nerve tube of modified Schwann cells form an adhesive surface for other nerve fibers growing out later, so that gradually an oriented path between the proximal and the peripheral stump is established. However, since the pioneering fibers have to traverse the relatively dense connective tissue of the scar and since this tissue does not seem to offer particularly favorable conditions for their growth, regeneration under those conditions remains always quantitatively inferior.

Exactly the same situation prevails when one of the stumps of a spliced nerve escapes from the sleeve. The sleeve, if it does not collapse entirely, becomes

12. Vulpius, O., and Stoffel, A.: Orthopädische Operationslehre, ed. 3, Stuttgart, F. Enke, 1924.

13. Ramón y Cajal, S.: Studien über Nervenregeneration, Leipzig, 1908.

14. Dustin, A. P.: Le rôle des tropismes et de l'odogénèse dans la régénération du système nerveux, Arch. de biol. **25**:269, 1910.

15. Weiss, P.: (*a*) Nerve Patterns: The Mechanics of Nerve Growth, Growth (supp.) **5**:163-203, 1941; (*b*) In Vitro Experiments on the Factors Determining the Course of the Outgrowing Nerve Fiber, J. Exper. Zool. **68**:393-448, 1934.

invaded by fibrous connective tissue no more advantageous for regenerating nerve fibers than ordinary scar tissue. Similarly, any break in the wall of the artery in the region of the splice impairs regeneration in a double way. In the first place, it permits the escape of fibers into the surroundings and, secondly, it opens the interior to the ingrowth of connective tissue from the vicinity of the nerve, which, in turn, leads to progressive fibrosis and strangling of the nerve fibers inside. A break in the arterial wall may be due to accidental injury during the operation or to later erosion of the wall as a result of infectious or autolytic processes. An example of each of these types is presented in figures 5 and 6.

Figure 5 shows the effect of a stab wound in the arterial wall made at the time of the operation. Owing to the lack of regenerative capacity of the artery this wound has remained open and has seriously affected the regenerative

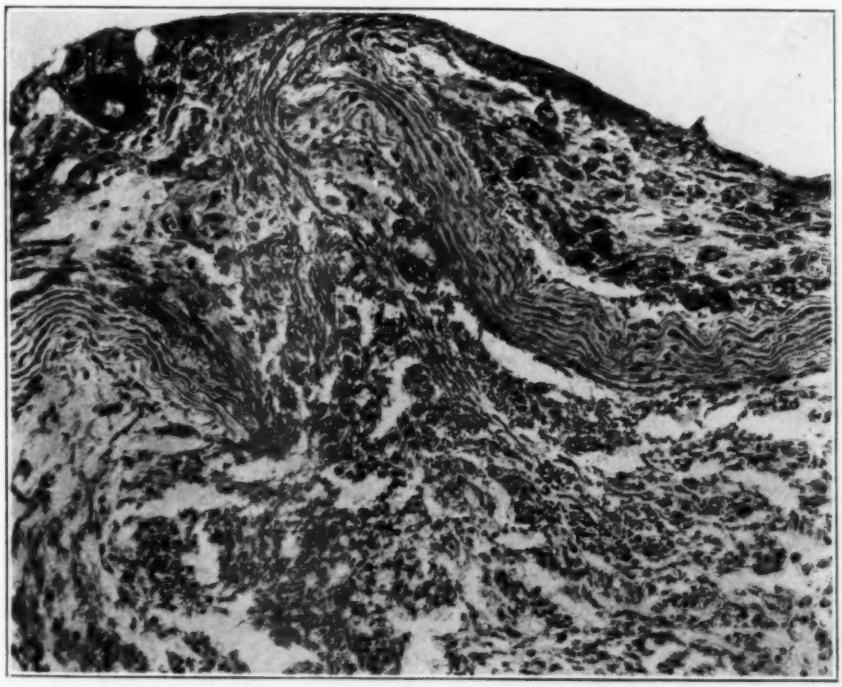


Fig. 5.—Effect of a leak in the arterial wall on regeneration of nerve fibers, thirty-eight days after operation. An explanation is found in the text (× 82).

processs of that area. Not only have the superficial fibers coming up along the perforated side of the wall escaped, but even deeper fiber masses have been deflected toward the leak. The picture one obtains in these cases resembles that of a streaming liquid escaping through a hole in the wall of a tube. Just as in the latter case eddies form—in the vicinity of the leak, so in the case of the nerve an extensive area of disturbance is set up within a certain radius of the opening, and in this area the nerve fibers leave their longitudinal course and converge on the hole. The mechanics of this disruption of the nerve pattern are apparently as follows: Blood plasma and lymph seeping through the hole after the operation coagulate in the direction of the flow and thereby establish a pathway into which the regenerating fibers may turn when they arrive at this level. Ingrowth of connective tissue from the outside along this same pathway, more-

over, produces a lateral adhesion, the tension of which further accentuates the local disorientation. Since nerve fibers have been demonstrated to follow such oriented pathways,[15b] a permanent outlet for part of the regenerating fibers is thus established.

Aside from distracting nerve fibers from their straight course, perforations are harmful in that they permit the invasion of fibrous tissue, which eventually establishes sclerotic islands inside the nerve. These, in turn, tend to choke nerve regeneration. While more detailed studies on the subject would be desirable, even our casual observations to date leave no doubt but that nerve fibers which lie embedded in this fibrous tissue remain very thin and immature. Even well oriented fibrous tissue is less pervious to nerve fibers than either degenerated nerve or the exudate of purely neural origin which fills the gap between the two stumps inside a well sealing arterial tube. Besides being a poor growth medium for nerve fibers, fibrous tissue may also be detrimental to the later functioning of nerve fibers contained in it, in that its progressive condensation may set up a pressure block interfering with conductivity.

In a good splice it is evidently the uninterrupted elastic layers that render the arterial wall escape-proof for nerve fibers. While in most experiments the arterial sleeves have retained their original texture throughout their length, a few have been observed in which circumscribed parts of the arterial wall had undergone more or less extensive dissolution. This may assume the aspect of either a local erosion from the outside or a gradual loosening up and swelling of the layers of the wall, with cells from the surroundings penetrating into the spongy mass. Whether these lesions are due to abrasions suffered in the operation or to infection cannot be said. At any rate, within these regions the arterial wall becomes porous, and as a result the pattern of nerve regeneration in such a region becomes thoroughly confused. Evidently, the porous condition of the wall, with the resulting transudation of tissue fluids and the release of longitudinal stress, causes again a widespread disorganization of the matrix inside the arterial lumen, within which the new nerve sprouts grow out, and this entails a complete disorientation of the nerve fibers in that vicinity.

Figure 6*A* shows a tangential section in the longitudinal direction of the nerve through one such area. The middle portion of the picture shows crisscrossing nerve fibers, many growing transversally and leaving the lumen of the artery by penetrating through the wall. To either side of the artery one can see a dense neuroma consisting of contorted nerve fibers from the escaped masses. In contrast to the effects of large holes discussed in the preceding paragraph, this porosity of the arterial wall, while permitting profuse dissipation of nerve fibers into the surroundings, does not seem to favor reciprocal inflow of fibrous tissue. Consequently, masses of nerve fibers which lie outside the immediately affected area, particularly those deeper in the interior of the nerve, regenerate as well as they otherwise do in intact arterial sleeves. This is illustrated in figure 6*B*. This figure shows a longitudinal section through the same nerve as figure 6*A*, slightly distal to the level of the former, traveling through the gap within the intact part of the artery. Here the fibers have remained confined within the tube and have regenerated in strictly parallel longitudinal orientation with no branching or confusion.

The great number of nerve fibers seen in and around an area of decomposition of the sleeve (fig. 6*A*) offers no correct gage of the actual loss of fibers as sources for refilling of the peripheral stump, for, firstly, their contorted course

in this area makes the same fibers appear several times in the same section, and, secondly, there is evidence of extensive branching, attributable to the wealth of obstructions to fiber growth in this region. Accordingly, the peripheral stumps of nerves with lateral eruption of fibers are not as badly depleted after regenera-

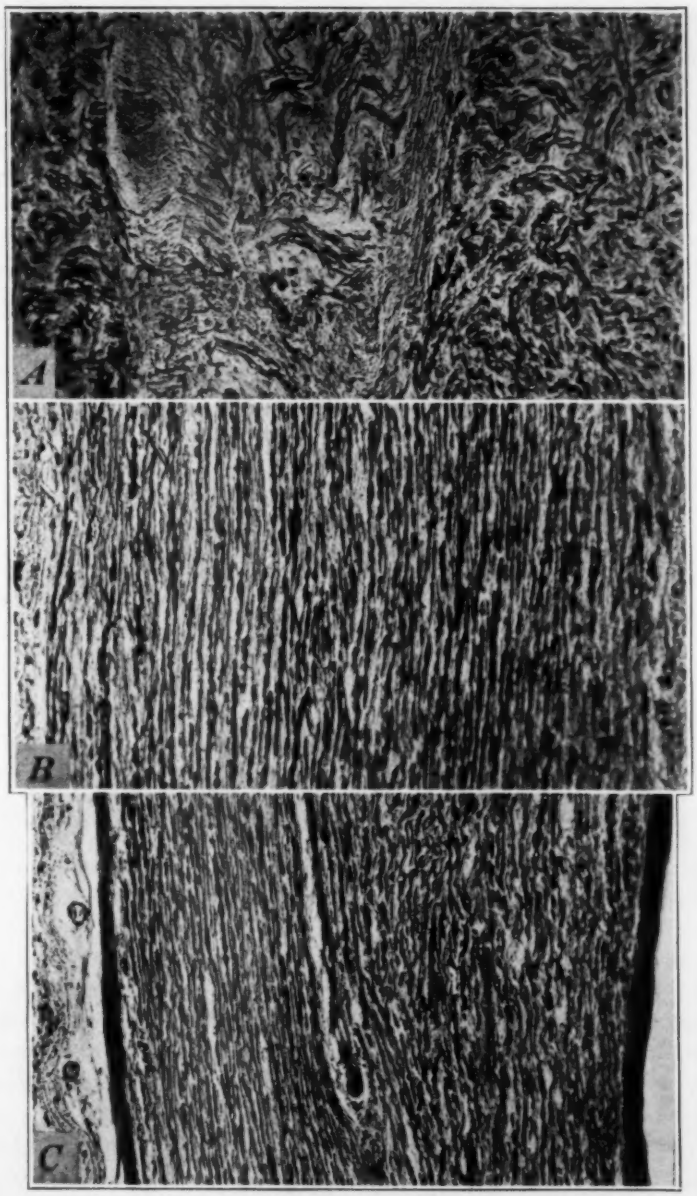


Fig. 6.—Effect of a local lesion in the arterial wall on growth of nerve fibers, one hundred and seventy days after operation. An explanation is found in the text (× 112).

tion as the size of these local neuromas would suggest. Figure 6 *C* shows a longitudinal section through the branching point between the peroneal and the tibial nerve (as in fig. 6 *A* and *B*). It shows the whole tract of the nerve filled

with regenerated fibers, and, while the total volume is slightly less than normal, it is not reduced nearly as much as one would have expected if the proximal fiber source had suffered a permanent reduction of such magnitude as figure 6 *B* would seem to indicate. Nevertheless, fiber counts on cross sections demonstrate that leaks in the artery wall do result in a certain permanent deficit of regenerated fibers in the peripheral stump. In one example, for instance, in which during the operation a lateral hole was made in the artery through which fibers later escaped, a fiber count proximal to the break of approximately 6,000 fibers dropped to approximately 2,200 fibers inside the nerve gap beyond the break, which figure rose only slightly farther distally to less than 2,600 fibers in the peripheral branches. Thus, while a negligible amount of regulative branching may have taken place, a definite deficit has remained.

Another type of failure results when a splice is made with arteries too small in diameter to accommodate the nerve without constriction. During the operation such arteries can, of course, be widened to the point where they can be forced over

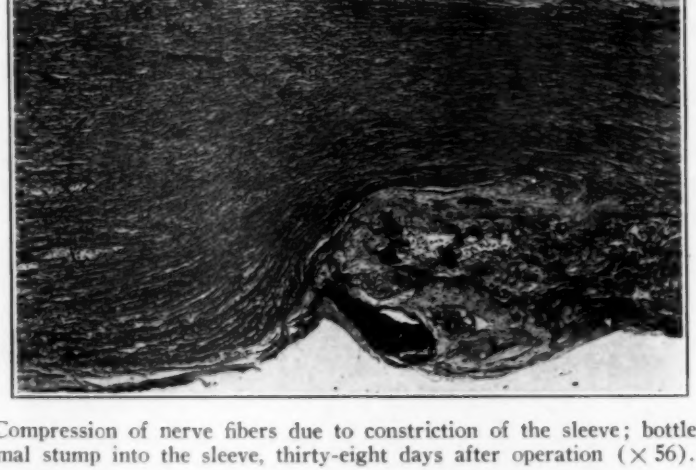


Fig. 7.—Compression of nerve fibers due to constriction of the sleeve; bottleneck at entry of the proximal stump into the sleeve, thirty-eight days after operation (× 56).

the nerve ends, but in postoperative stages they contract again and strangle the nerve in the interior. When this happens, the effects on the nerve are serious. The histologic appearance of such a regenerate is exemplified in figure 7, showing the proximal end of a constricted arterial sleeve. As one can readily see, the sleeve forms a bottleneck, inside of which the nerve fibers are condensed into a tightly packed bundle. Moreover, the proximal stump of the nerve is for some distance proximal to its entrance into the sleeve pathologic in appearance. A conspicuous edema is formed here, which gives the nerve a bulbous shape. The inside of the nerve is loosened up, fibers and fiber bundles are widely separated and retrograde degeneration has proceeded farther centrally than is found after mere nerve section. The edema proximal to the constriction is of great interest. It clearly demonstrates that there is normally in the nerve a centrifugal flow of "lymph." Obstructed by the tight packing of the fibers in the sleeve, this flow is arrested and the dammed-up fluid distends the nerve. A similar observation,

namely, an edematous condition of the nerve stump in constricted human nerves, has been reported by Dustin.[16]

Close inspection of the nerve fibers passing through the bottleneck reveals an abrupt change of their size and condition at the level of constriction. Proximal to this level there are many large fibers in advanced stages of maturation, while within the constricted area all fibers are small and immature, like those of very young regenerates. This does not mean that the large fibers have grown only as far as the level of the constriction and there become arrested, but rather that one and the same fiber has assumed large diameter in the proximal part but remained small and undeveloped within the compressed area. This could be ascribed to a sort of inanition effect resulting from the lymph stasis mentioned before, but it is more likely due to the obstruction of the centrifugal flow in the axis-cylinders themselves of some essential factor produced by the nerve cell body and required for continued growth in width of the peripheral fiber. This is suggested by the fact that the fibers just proximal to the level of constriction are often swollen and club shaped, as if some substance passing down the axon had become dammed up on the inside.[17]

The few such constrictions observed thus far were studied only five to six weeks after the operation. Therefore, it is impossible as yet to say whether the immaturity and small size of regenerated fibers under lateral compression are a permanent feature. However, in view of the tight packing of the fibers and the apparently firm stranglehold of the artery, it may be considered doubtful whether these fibers will ever have an opportunity of acquiring larger caliber. Some of these compressed nerves have been studied oscillographically and will be discussed on a later occasion. It may suffice here to say that this condition seems to set up a definite pressure block interfering with conduction along those fibers. Therefore, although complete neurotization of the peripheral stump may be obtained even under these conditions, the functional results of such regeneration are rather inadequate.

It is evident, then, that most failures of the arterial splice are due to improper manipulation during the operation or to the selection of arteries which are either too big, and thus admit extraneous fibrous tissue, or too small, and thus choke the nerve.

COMMENT

Properly executed, the arterial splice leads to a satisfactory reunion between proximal and peripheral stump and creates most favorable conditions for subsequent nerve regeneration, provided the two cut surfaces can be brought within fair proximity. It can be applied wherever there is enough slack on the nerve to permit apposition of the cut surfaces. However, intimate contact between the two ends is neither necessary nor desirable. Pressing the two ends together so as to produce flanging forces the nerve fibers into a tangle which a good suture tends to avoid. Moreover, it must be borne in mind that regeneration of the fibers does not actually start from the level of apposition but begins slightly more proximally, since a variable and uncontrollable amount of retrograde degeneration is bound to precede the onset of regeneration.

It has already been pointed out by Nageotte [5] that a slight gap between the nerve stumps is advantageous for regeneration, and the same general conclusion

16. Dustin, A. P.: Les lésions posttraumatiques des nerfs: contribution à l'histopathologie du système nerveux périphérique chez l'homme. Ambulance de "l'Ocean," 1917, vol. 1, pt. 2, pp. 71-161.

17. Parker, G. H.: On the Trophic Impulse So-Called: Its Rate and Nature, Am. Naturalist **66**:147-158, 1932.

must be drawn from the present experiments. The size of the gap in our experiments can be reconstructed from longitudinal sections as the distance between the margins of the proximal and the distal epineurium. The epineurium, at least under the conditions of our experiments, has shown little tendency to regenerate, and its edges, therefore, mark the limits of the old nerve stumps rather distinctly. If these landmarks are used and allowance is made for the fact that they may have been slightly retracted during the healing process, it becomes evident that a gap up to 3 mm. between the original nerve ends is compatible with good nerve regeneration. Through such a gap regeneration takes place with the same strict orientation, fiber alinement and ease as if the fibers were proceeding inside a degenerated peripheral stump. Larger gaps have not been found equally passable, primarily for the reason that the arteries in such regions, lacking a solid core, tend to collapse so that their lumen becomes partly obstructed.

The question now arises as to what forms the matrix, i. e., the medium in which the nerve fibers grow while traversing the gap. Obviously the gap is no void but is filled with substance even before the regenerating nerve fibers arrive, and the composition and properties of this substance become a matter of great interest in that they seem to be exquisitely favorable for nerve growth. Save for the few instances with postoperative intraneural bleeding, no large blood clot was present between the stumps, and therefore the matrix of the gap does not consist of blood plasma. The tight fit of the arterial sleeve and its sealing to the nerve by rapid clotting prevent the seeping in of extraneous fluid. This seems to leave the interior of the nerve as the sole source of whatever medium fills the gap. It may be assumed to be primarily composed of an exudate of intraneural "lymph," possibly carrying additional products exuded from the severed nerve fibers and sheath cells. The connective tissue cells in the nerve do not seem to be numerous enough to be credited with a sizable contribution. That this nerve exudate is a reality has recently been demonstrated in tissue culture experiments in which embryonic ganglions and nerves were reared at the phase boundary between a cover slip and a liquid medium. It was noted that if the medium consisted of Tyrode's solution with or without a trace of blood serum added a film of substance would seep out from the living tissue along the phase boundary and that outgrowing nerve fibers would tend to hold themselves within that film. On fixation and impregnation with silver salts, the film reveals a fine reticulated structure, which would suggest that it contains fiber proteins or other fiber-forming elements capable of oriented aggregation. While much of this work is still in the exploratory stage, it definitely points in the same direction as the splicing experiments, namely, that nerve tissue when injured produces an exudate capable of becoming oriented and obviously most favorable, in biophysical and biochemical regards, for rapid nerve growth.

The role of the colloidal matrix in which nerve growth takes place has been discussed in earlier papers.[18] The orientation of nerve growth has been resolved essentially into a matter of the orientation of the surrounding colloidal particles plus the tendency of the growing nerve fiber to comply with this orientation of its surroundings. The exudate which accumulates between the nerve stumps is evidently capable of assuming such orientation and thereby serving as an oriented guiding substratum for the outgrowing nerve fibers. In this respect it seems not to differ significantly from fibrin clots, which were used in the earlier experiments on

18. Weiss.[15] Harrison, R. G.: The Croonian Lecture on the Origin and Development of the Nervous System Studied by the Methods of Experimental Embryology, Proc. Roy. Soc., London, s.B **118**:155-196, 1935.

nerve fiber orientation and more recently by Young with good success for the union of severed nerve stumps. However, the tendency of the fibrin clot to become converted into dense connective tissue, with all the disadvantages such fibrosis entails for nerve growth, is absent in the exudate of nervous origin. Comparative studies are under way to determine whether the difference between a fibrin filling and a neural exudate in the lumen of the arterial splice is sufficiently pronounced to have practical significance.

I have said the matrix inside the sleeve is capable of becoming oriented, that is, it is presumably composed of rod-shaped polar ultramicrons. To orient these, an orienting factor is required. This factor is provided by the longitudinal tension to which the nerve is subjected. The effect of such tension on a potentially fiber-forming matrix has been described earlier.[19] It forces the ultramicroscopic fibrillar units into parallel alinement. This has two consequences: First, it compels cells of the spindle type, i. e., fibrocytes as well as sheath cells, to extend in a similar direction, and, secondly, it orients the growth of the nerve tips accordingly. In regeneration this has the effect of presenting the nerve fibers with a system of guide rails along which the outgrowing sprouts can continue in a direct straight course, passing on without obstruction into the open tubes of the peripheral stump. At the same time this longitudinal organization prevents the formation of oblique or transverse patterns which would deflect the nerve fibers from their straight course and, in addition, cause profuse branching.

Nageotte [5] has asserted that growth of sheath cells from the peripheral stump centrad precedes the outgrowth of the nerve fibers. I have made no study of the early stages of regeneration in my experiments to test this point. If it should prove correct, the orientation of the gap region would have its primary effect on the hyperplastic sheath cells in that it would force them into straight line connections between the proximal and distal stumps, which then, in turn, would serve as invasion routes for the outgrowing nerve sprouts. It is likely that the orientation of the matrix straightens nerve growth both indirectly, by way of the sheath cells, and directly, by orienting nerve fibers advancing freely. At any rate, the unconfused and strictly oriented pattern of the regenerating fibers must be ascribed in last analysis to the tension in longitudinal direction which the nerve exerts on the matrix that seals its two ends.

It may be pointed out that most suture methods in which the two stumps are united by rigid threads fail to accord the area of regeneration the benefit of this longitudinal strain. Longitudinal stresses arising in nerves held together by silk sutures are taken up by the rigidity of the suture material or at best by the rather unelastic epineurium. This leaves the interior between the ends of the suture slack, and the region which needs longitudinal strain most for a good orientation of nerve growth has the least of it. The plasma suture of Young and his co-workers is the only other method in which the gap region is accorded the full advantage of longitudinal stress in the nerve. However, since such tension, while highly desirable for regeneration, is undesirable during the early stages of suture in that it may rupture the fresh union, the fibrin method has its well recognized limitations. The arterial splice, on the other hand, in providing a firm seal between the arterial segment and the two nerve stumps, yet being elastic enough to withstand considerable extension, reduces the danger of rupture while allowing full play to the orienting action of longitudinal strain.

19. Weiss, P.: Functional Adaptation and the Role of Ground Substances in Development, Am. Naturalist **67**:322-340, 1933; footnote 15 *b*.

It must be kept in mind that the favorable results thus far obtained with this method have been proved valid only within the limits within which they have been tested, namely, for the nerves of the rat, which are comparatively small. How the method will work out with larger nerves and in higher mammals, including man, is a question that cannot be answered until the results of an extensive series of experiments being carried out at the present time have become known. But it is obvious that even if the method should fail on large nerves, it is still uniquely suited for the mending of small nerves which defy ordinary suture methods on account of their small caliber.

For reasons already mentioned the method is not indicated for reunion of severed nerves in cases in which either loss of substance or considerable retraction of the stumps has created a sizable gap. To repeat, the arterial sleeve does not serve as a conduit for nerve fibers over appreciable distances, although it does help to bridge small gaps, of a few millimeters, or, in terms of the size of the nerve, a length not exceeding the diameter. In the case of larger gaps, nerve grafts will have to be used as heretofore. Again, however, the union between the graft and the two nerve stumps is to be effected with the aid of arterial splices, one such splice uniting the proximal end of the graft to the proximal stump and the other the peripheral stump to the distal end of the graft. The longitudinal stress on the nerve tends to prevent the formation of a glial scar, fibrous ingrowth and constriction at the distal suture line, so that by the time the regenerating nerve fibers have reached this level they should find a smooth and well organized pathway for transit into the peripheral stump, instead of the impassable fibrous bulkhead often encountered at the distal suture line. Experiments to demonstrate this point are under way.

A point of great practical significance is the choice of the artery. The importance of correct caliber has been previously discussed. Another feature to be considered is the amount of musculature in the arterial wall. What is really needed for a successful splice is merely the tough and impenetrable layers of elastic tissue. It is to these that the artery owes the properties that make it so suitable for the purpose. The muscular tissue, if anything, is harmful. While no detailed study has yet been made of this point, it seems that the circular musculature of the artery may receive reinnervation from autonomic fibers in the region of the wound and resume contractions. Even without such innervation a spasm of the muscular wall could develop which would strangle the nerve in the arterial lumen. As a matter of fact, the constrictions described as causes of failure were probably in part due to a secondary reduction of the arterial lumen by the contraction of the muscular coat. Pending a more systematic investigation of the subject, it may be said, therefore, that an artery will be the better suited for the purpose of splicing nerves the smaller the amount of muscular tissue in proportion to the volume of elastic tissue present.

Veins do not seem to be the equal of arteries as splicing agents. Their wall easily becomes porous and pervious, with all the detrimental consequences to nerve regeneration discussed for accidentally perforated arteries.

Experiments exploring the possibility of using arteries stored in various ways are under way. The use of arteries fixed by ordinary histologic means, as with alcohol or solution of formaldehyde, is contraindicated. Such preserved arteries have been used repeatedly in the past for the purpose of "tubulating" nerve regeneration, but the loss of elasticity caused by the treatment makes such tubular fragments wholly unsuitable for the purpose of splicing. Means by which arteries can

be stored under sterile conditions for long times without losing either their elastic properties or their laminated texture, both of which are prerequisites for successful splicing, will be reported on a later occasion.

SUMMARY

A method is reported by which severed nerve stumps can be united without the use of sutures. It consists in sealing the nerve ends into a common tightly fitting sleeve of live artery. Histologic evidence is presented, based on experiments on rats, showing that when this method is used (1) a firm tie between the stumps is obtained which has adequate tensile strength and offers most favorable conditions to nerve fiber regeneration; (2) nerve fibers regenerate in straight parallel courses; (3) regenerating fibers do not branch, nor do they stray about, intermingle, escape from the nerve or form local neuromas; (4) regenerating fibers essentially retain their mutual topographic relations; (5) ingrowth into the nerve of fibrous connective tissue and strangling of nerve fibers by fibrosis are prevented; (6) no fibrous scars form at the suture lines, and (7) even the smallest nerves can be mended.

ROLE OF TOXIN AND USE OF ANTITOXIN IN SYSTEMIC STAPHYLOCOCCIC INFECTIONS

BARNARD KLEIGER, M.D.
AND
JOHN E. BLAIR, PH.D.
NEW YORK

Since it is now recognized that some strains of staphylococci produce a potent exotoxin, it is important to correlate experimental studies of staphylococcus toxin with clinical observations on systemic staphylococcic infections which have been previously reported. The exotoxin is capable of producing several well defined effects on different tissue cells, but it has never been adequately demonstrated whether these effects are due to several different tissue-specific toxins or whether a single toxin affects each tissue differently. Nevertheless, the outstanding results of the action of staphylococcus exotoxin are: hemolysis of red blood cells (hemolysin), destruction of leukocytes (leukocidin), necrosis of skin and subcutaneous tissues on direct injection (dermonecrotoxin), rapid death of laboratory animals on intravenous injection (lethal factor), necrosis of certain other tissues, such as the renal glomeruli and the mucous membranes of the gastrointestinal tract, and irritation of the synovial membrane on injection into joints.[1]

Effect of Toxin in Vivo on Laboratory Animals.—Following the intravenous injection of a lethal dose of a potent staphylococcus toxin, free from staphylococci, into laboratory animals, a characteristic chain of events has been repeatedly observed.[1a] Within a few minutes after the injection the animal becomes weak or the hindlegs are paralyzed; the respirations become shallow and irregular, and the animal weakens to such an extent that it can no longer stand erect and rolls onto its side. Before death the animal has violent convulsions and the legs execute strenuous running movements. At death the animal goes into opisthotonos, and terminally expels urine or feces or both. Accompanying these symptoms in rabbits Joyner and his associates [2] have observed a marked increase of young myeloid cells in the bone marrow and proportionately in the circulating blood.

These symptomatic effects are associated with a severe cardiovascular response. Electrocardiographic changes indicating myocardial damage have been observed in laboratory animals by Nélis, Bouckaert and Picard [3] and by Dingle, Hoff, Nahum and Carey.[4] We have been able to confirm these changes in rabbits, and accompanying them we have seen a characteristic pattern of variations in the pulse rate.[5] Immediately after the intravenous injection of toxin the pulse rate under-

From the Laboratory Division, Hospital for Joint Diseases.

1. (*a*) Blair, J. E.: The Pathogenic Staphylococci, Bact. Rev. **3**:97 (June) 1939. (*b*) Rigdon, R. H.: Staphylococcus Toxin: A Résumé, Am. J. M. Sc. **199**:412 (March) 1940.

2. (*a*) Joyner, A. L.: Personal communication to the author. (*b*) Joyner, A. L.; Rigdon, R. H., and Hare, R.: A Study of the Effects of Staphylococcus Exotoxin on Leucocytes and Bone Marrow of Rabbits, J. Bact. **33**:47 (Jan.) 1937.

3. Nélis, P.; Bouckaert, J. J., and Picard, E.: Contribution à l'étude de la toxine staphylococcique, Ann. Inst. Pasteur **52**:597 (June) 1934.

4. Dingle, J. H.; Hoff, E. H.; Nahum, L. H., and Carey, B. W., Jr.: The Effect of Staphylococcus Aureus Exotoxin on the Rabbit Heart, J. Pharmacol. & Exper. Therap. **61**:121 (Oct.) 1937.

5. Kleiger, B.; Blair, J. E., and Hallman, F. A.: Behavior of Rabbits After Infection with Toxigenic and Nontoxigenic Staphylococci: An Experimental Study, Arch. Surg. **45**:571 (Oct.) 1942.

goes a transient depression; this is soon followed by an increase in rate to about 50 to 100 beats per minute above the normal. As the summit of the increase is reached the pulse rate drops sharply, and with this the electrocardiographic changes previously mentioned appear.

Toxin Production in Vivo in Laboratory Animals.—Toxigenic staphylococci will produce exotoxin in vivo in laboratory animals, and the disease caused by the intravenous injection of these organisms in rabbits is different from the disease produced by nontoxigenic staphylococci similarly injected.[5] About twenty hours after the injection of a saline suspension of a culture of a toxigenic strain of staphylococci that had been thoroughly washed to remove any traces of free toxin there began the same characteristic chain of events that had been observed, in more rapid sequence, in animals which had received injections of toxin alone. The animals died within twenty-four hours in convulsions and in opisthotonos. The changes in the electrocardiogram and in the pulse rate were the same as those following the injection of toxin.

The reaction of rabbits to the intravenous injection of a saline suspension of a washed culture of nontoxigenic staphylococci was different from the reaction of animals which received toxigenic staphylococci. These rabbits also died within twenty-four hours. However, after about twelve hours they became lethargic, and then became progressively weaker until at some time between twelve and twenty-four hours they died quietly. At no time did they have violent convulsions, nor did they go into terminal opisthotonos. There were no electrocardiographic changes, nor was there any characteristic pattern of variation in the pulse rate.

Variations in immunity alter the response of an animal to infection by toxigenic staphylococci. In 1 animal so infected none of the characteristic symptoms of toxicity occurred; numerous abscesses developed, the rabbit's condition gradually deteriorated and after several days it died. None of the characteristic changes in the electrocardiogram or in the pulse rate developed. This picture was duplicated by administering adequate amounts of staphylococcus antitoxin to rabbits infected with toxigenic staphylococci.

Effect of Toxin in Human Beings.—The clinical importance of staphylococcus toxin first attracted wide attention after the disaster at Bundaberg, Australia, in 1928.[6] Twenty-one children were given a prophylactic dose of diphtheria toxin-antitoxin, and within thirty-six hours 12 of the 21 succumbed to a fulminating systemic disease characterized by diarrhea and rectal incontinence, a high fever and a rapid pulse rate out of proportion even to the elevated temperature. The patients rapidly went into coma, soon became completely irrational and died in delirium. In the children who survived abscesses developed later at the site of injection. From the abscesses was cultured the same strongly toxigenic hemolytic Staphylococcus aureus that was cultured from the single bottle of toxin-antitoxin which had been used for all the children.

Since such close resemblance exists between the symptoms of animals dying of the effects of staphylococcus toxin and the symptoms of the children who died in the Bundaberg disaster, it appears that in persons who are susceptible to the toxin infection by toxigenic staphylococci causes a chain of symptoms which are peculiar to the toxin. This has been demonstrated in a previously reported study,[7]

6. Kellaway, C. H.; MacCallum, P., and Tebbutt, A. H.: Report of the Royal Commission of Enquiry into the Fatalities at Bundaberg, M. J. Australia **2**:2 (July 7); 38 (July 14) 1928. Foreign Letters (Australia), J. A. M. A. **91**:262 (July 28) 1928.

7. Kleiger, B., and Blair, J. E.: Correlation Between Clinical and Experimental Findings in Cases Showing Invasion of the Blood Stream by Staphylococci, Surg., Gynec. & Obst. **71**:770 (Dec.) 1940. Kleiger, B.: Granulocytopenia Following Acute Staphylococcal Osteomyelitis, Bull. Hosp. Joint Dis. **2**:180 (Oct.) 1941.

in which we concluded that it is possible to determine from the clinical characteristics alone whether the symptoms are manifestations of disease due to the staphylococcus toxin or to other factors in staphylococcic infection. The onset of true staphylococcic toxemia in human beings is rapid, and the initial manifestations are systemic rather than local. The most frequent of these are abdominal pain, diarrhea, incontinence of feces or urine or both, meningismus, coma and delirium. These symptoms are acute during the first four or five days of illness, and the sooner they reach their maximum acuity the more pronounced has been the effect of the toxin on the patient. The pulse rate rises rapidly to a height out of proportion to the height of the temperature. In the most toxic patients the rate stays above 140 beats per minute. The importance of a low white blood cell count with a relative increase in the number of nonsegmented cells has been stressed as an index of toxicity.[8] We have found this to be of value as confirmatory evidence, but we depend to a greater degree on the clinical picture.

We have never found this picture in patients over 30 years of age, and therefore we have come to feel that such persons are more resistant to the systemic effects of the toxin. Thus, in older persons the disease develops more slowly and at first the symptoms are those arising from the local infectious lesion. To these are added later the symptoms of the disturbed metabolic processes associated with long-standing illness. The temperature may be greatly elevated, but in spite of this the pulse rate will not exceed 120 beats per minute early in the disease; however, circulatory embarrassment may occur later, and then the pulse rate will rise above 140 beats per minute. The prognosis in this group of patients usually depends on the health of the individual prior to his infection and on the site of local or metastatic lesions. Death results only when predisposing or intercurrent illness so weakens the patient that he is unable to withstand the onslaught of the infection, or when the infection attacks some vital organ or a region that cannot be satisfactorily drained surgically.

The Therapeutic Use of Antitoxin.—Since toxin plays an important role in certain staphylococcic infections, a potent specific antitoxin should be of therapeutic value.[9] Antitoxin cannot be employed indiscriminately for all types of staphylococcic infection, particularly those which are chronic or refractory to other forms of therapy; its use must necessarily be confined to those acute conditions in which the effects of toxin are clinically apparent.[10] The dosage should be adjusted to the degree of toxicity as well as to the size of the patient, somewhere between 1,000 and 2,000 units of antitoxin per pound (between 2,200 and 4,400 units per kilogram) of body weight being required for the first day. This dose is then reduced each succeeding day to just the amount necessary to control the patient's symptoms. It should not be necessary to continue the administration of antitoxin beyond the

8. (*a*) Baker, L. D., and Shands, A. R., Jr.: Acute Osteomyelitis with Staphylococcemia: Clinical Report on the Use of Antitoxin in Its Treatment, J. A. M. A. **113**:2119 (Dec. 9) 1939. (*b*) Baker, L. D.: Acute Osteomyelitis with Staphylococcus Septicemia, South. M. J. **34**:619 (June) 1941. (*c*) Joyner, A. L., and Smith, D. T.: Acute Staphylococcus Osteomyelitis: The Use of Staphylococcus Antitoxin as Aid to Management of Toxemia and Staphylococcemia, Surg., Gynec. & Obst. **63**:1 (July) 1936. (*d*) Joyner.[2a] (*e*) Joyner, Rigdon and Hare.[2b]

9. Dolman, C. E.: Staphylococcus Antitoxic Serum in the Treatment of Acute Staphylococcal Infections and Toxaemias, Canad. M. A. J. **30**:601 (June) 1934; **31**:1 (July); 130 (Aug.) 1934.

10. (*a*) Stookey, P. F., and Scarpellino, L. A.: Staphylococcus Septicemia, South. M. J. **32**:173 (Feb.) 1939. (*b*) Baker and Shands.[8a] (*c*) Baker.[8b] (*d*) Dolman.[9] (*e*) Joyner and Smith.[8c]

fourteenth day of the patient's illness, by which time the blood should contain a sufficiently high antitoxin titer.[11]

As with any type of serum therapy, the potential dangers of serum reactions always exist.[12] These reactions may be immediate or delayed. The most common and the least serious immediate reaction is thermal. Shortly after the injection of serum the patient feels chilly or undergoes a definite shaking chill; this is followed by a sharp rise in temperature, and may be accompanied by an increased pulse and respiratory rate and a varying degree of circulatory and respiratory collapse. The other immediate reactions are less frequent, but more serious. True anaphylaxis is always alarming and is often fatal. The symptoms are usually those accompanying rapid paralysis of the respiratory and circulatory centers. Another serious immediate reaction is the occasional occurrence of peripheral circulatory failure following the injection of serum. This usually occurs in persons with previously existing cardiovascular disease. The delayed serum reaction is the common serum sickness which appears seven to ten days after injection, and is characterized by urticaria, arthralgia and malaise. This form is readily controlled and requires little discussion.

For the administration of staphylococcic antitoxin we have adopted the following routine, which has been eminently successful. We first inject 0.1 cc. of undiluted antitoxin intracutaneously into the flexor surface of the forearm. Fifteen minutes later, if no reaction has occurred in the form of a wheal or formation of pseudopods surrounding the site of the injection, 2 or 3 cc. is injected intramuscularly into the buttock. Two hours later an intravenous infusion of 5 per cent dextrose in physiologic solution of sodium chloride is started. To the infusion fluid is added sufficient antitoxin to make a dilution of about 1:15. The serum is dispensed in vials each containing 20,000 units of antitoxin. It has been our practice to compute the total dose required for each day, and then to give 20,000 units at regular intervals until the required amount for that day has been administered. If the patient reacts positively to the cutaneous test, he is desensitized by the intramuscular injection, at intervals of one-half hour, of 2 cc., 3 cc., 5 cc. and 10 cc. of antitoxin. Desensitization is followed by the administration of antitoxin by the intravenous method just described, which is started about one to two hours after the last desensitizing dose. When serum preparations are being administered, epinephrine or ephedrine should always be available for immediate use.

Staphylococcus antitoxin when used in patients whose symptoms were actually due to toxin has brought about a most gratifying clinical improvement. Within twelve hours from the onset of therapy children whose symptoms had been fulminating became quiet and rational. Diarrhea and fecal and urinary incontinence

11. (*a*) Stookey, P. F.; Scarpellino, L. A., and Weaver, J. B.: Immunology of Osteomyelitis, Arch. Surg. **32**:494 (March) 1936. (*b*) Weiss, C.: A Study of Natural and Acquired Immunity to Staphylococcal Toxin in Monkeys, J. Immunol. **37**:185 (Sept.) 1939; (*c*) Availability of Staphylococcal Antitoxin After Intramuscular Injection into Normal Monkeys and Man, Proc. Soc. Exper. Biol. & Med. **43**:441 (March) 1940; (*d*) Serum Antistaphylolysin Titers During Antitoxic Therapy of Staphylococcal Infections, Am. J. Clin. Path. **11**:329 (April) 1941. (*e*) Stookey and Scarpellino.[10a]

12. (*a*) Besredka, A., and Gloyne, S. R.: Anaphylaxis and Anti-Anaphylaxis, and Their Experimental Foundations, St. Louis, C. V. Mosby Company, 1919. (*b*) Mackenzie, G. M.: Serum Disease and Serum Accidents, in Cecil, R. L.: A Textbook of Medicine, ed. 3, Philadelphia, W. B. Saunders Company, 1934. (*c*) Rutstein, D. D.; Reed, E. A.; Langmuir, A. D., and Rogers, E. S.: Immediate Serum Reactions in Man: Classification and Analysis of Reactions to Intravenous Administration of Antipneumococcus Horse Serum in Cases of Pneumonia, Arch. Int. Med. **68**:25 (July) 1941.

ceased, and the pulse rate was reduced to a level in proportion to the temperature. The white blood cell count later rose to 15,000 to 20,000, and the number of nonsegmented cells diminished. Antitoxin has no direct effect on the staphylococcus or on the infection, but the neutralization of toxin doubtless aids nonspecific antibodies in combating and localizing the infection.[1b]

The results of antitoxin therapy have in a manner confirmed our previous observations that true staphylococcic toxemia is associated with a characteristic clinical picture. More specifically, the patients exhibiting the characteristics of a true toxemia responded rapidly and well to the administration of staphylococcic antitoxin. Conversely, patients above the age of 30 and others who did not show evidence of toxemia did not respond to antitoxin in this manner.

Our present therapeutic approach has been followed only since December 1939. Since then we have treated, without a single death, 4 children with definite toxic symptoms and bacteremia and 4 with mild to moderate toxicity and bacteremia. Three other children who were similarly treated also survived; 1 of these had obvious toxic symptoms and bacteremia, and 2 had moderately toxic symptoms, but their blood cultures remained sterile. These 3 patients are mentioned separately because of insufficient data for a complete study. A laboratory study of the staphylococci isolated from material obtained from 9 of the patients confirmed the correlation between the toxigenicity of the organism and the character of the clinical symptoms which we had previously observed. All of these patients were treated with what we considered to be adequate amounts of a commercial staphylococcus antitoxin.[13] Additional treatment in the form of transfusions, fluids and sedation was given as indicated. Sulfonamide compounds in the form of thiazole derivatives and sulfadiazine were given at some stage in the majority of the cases, but their value cannot be properly estimated. In no instance did a prompt remission follow the administration of a sulfonamide compound, and the course of the patients treated with sulfonamide compounds did not differ from that of the patients in whose cases the drugs were not used. On the basis of the clinical response we feel quite certain that the sulfonamide compounds have no clinical effect on the toxic phase of staphylococcic infections.

We can probably best illustrate the effectiveness of antitoxin by describing the response of 2 children with definitely toxic symptoms who received adequate amounts of the antitoxin without the concurrent use of sulfonamide compounds.

REPORT OF CASES

Case 1.—A 7 year old boy, previously reported on by Dr. Carroll M. Silver before the Clinical Society of this hospital,[14] was admitted on the third day of illness with acute hematogenous osteomyelitis of the upper end of the tibia and staphylococcic bacteremia. His temperature was 105.2 F. and his pulse rate 155 beats per minute; he was comatose, completely irrational and incontinent of feces. Antitoxin was administered according to the technic described, with no serum reaction. Within twelve hours the boy received 120,000 units of antitoxin and by the end of that time he was mentally clear and alert and able to take fluids. By the next morning the pulse rate was 120 and the temperature was 100 F., and from then on recovery was uneventful. He was given 340,000 units of antitoxin in five days. Chart 1 shows the pulse and temperature records for the first fourteen days of hospitalization.

13. Mr. S. D. Beard of the Lederle Laboratories, Inc., made available a generous supply of Staphylococcus Antitoxin (Lederle) for this work.

14. Silver, C. M.: Staphylococcus Bacteremia with Osteomyelitis: Problems and Treatment, paper read at the meeting of the Clinical Society, Hospital for Joint Diseases, Oct. 7, 1941.

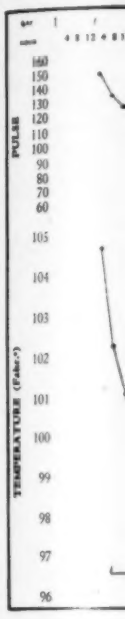


Fig.
period
by T.

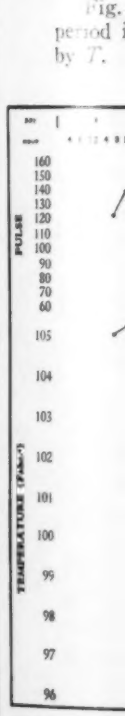


Fig.
indicat

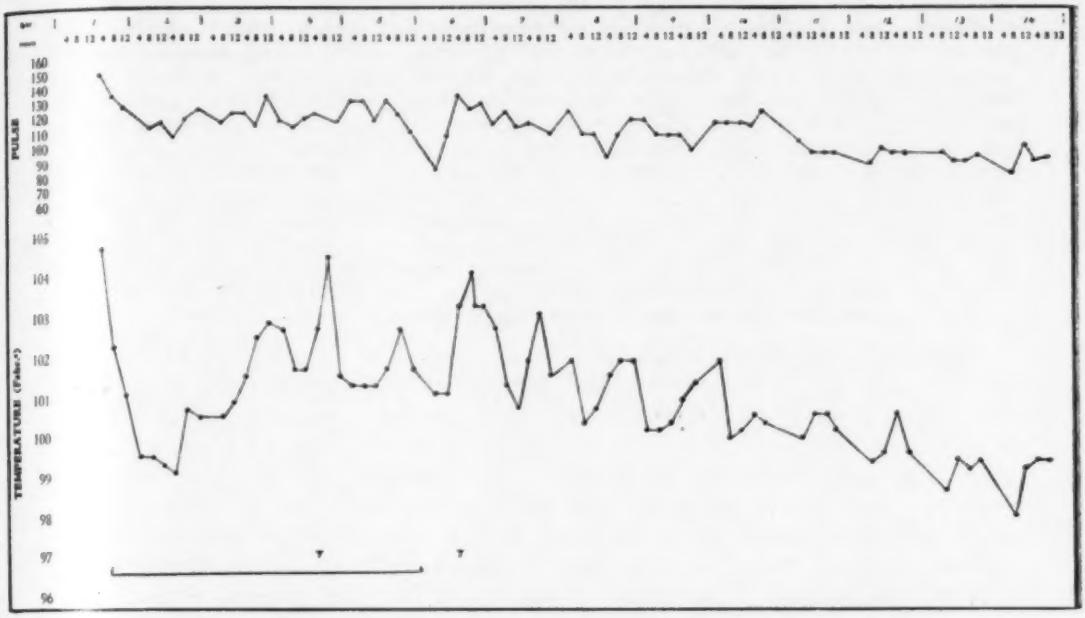


Fig. 1.—Pulse and temperature record in case 1. Antitoxin was administered over the period indicated by the solid line at the bottom of the chart. Blood transfusions are indicated by *T*.

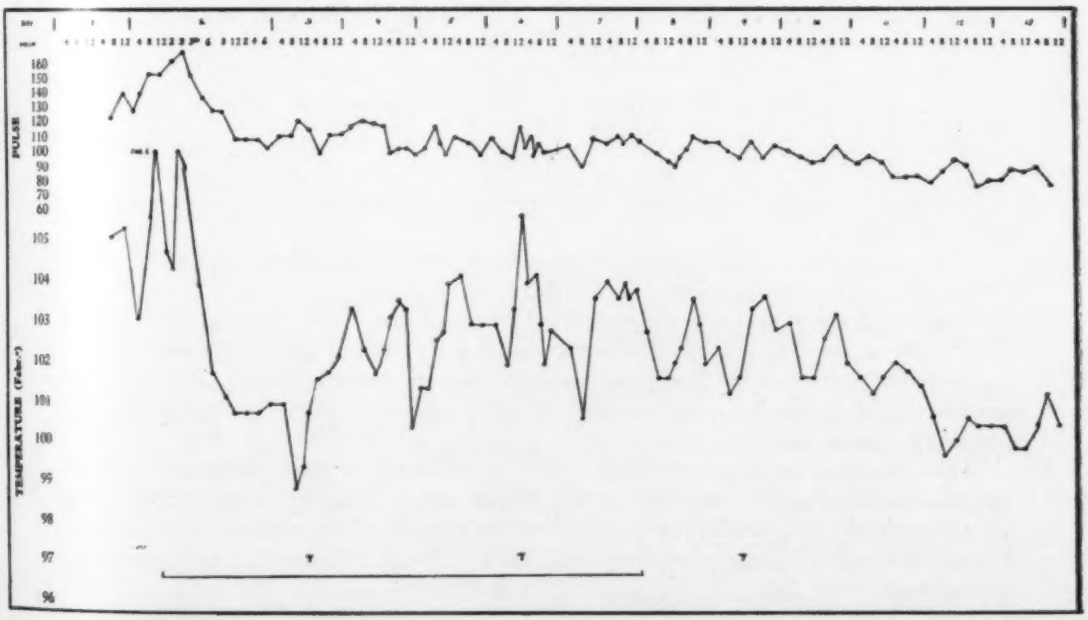


Fig. 2.—Pulse and temperature record in case 2. Antitoxin was administered over the period indicated by the solid line at the bottom of the chart. Blood transfusions are indicated by *T*.

CASE 2.—A girl of 9 years was admitted to the hospital after one day of illness with acute osteomyelitis of the upper end of the tibia and staphylococcic bacteremia. On her admission the temperature was 105.6 F., the pulse rate was 128 and she appeared to be only moderately toxic. By the next morning her temperature had risen to 108.6 F. and the pulse rate to 156, and she was completely irrational and unresponsive. Twenty thousand units of antitoxin was given by the recommended technic with no serum reaction. However, it was felt by the attending physicians that the serum should be administered more rapidly, and a second dose of 20,000 units was given undiluted by vein. This was followed by a severe thermal reaction, consisting of chills, convulsions and a one minute period of total apnea. Her temperature then rose again to 108.6 F., and the pulse rate to 168 beats per minute. She recovered from the reaction, and two hours later we resumed intravenous serum therapy by the proper technic. One hundred and forty thousand units was given on the first day, and within twelve hours her temperature was 101.2 F., the pulse rate was 118, and her symptoms were greatly improved. For two days she had periods of disorientation, but recovery proceeded. This child was given 480,000 units of antitoxin in six days. Chart 2 shows the pulse and temperature records for the first thirteen days of hospitalization.

Such results are in sharp contrast to those obtained in a comparable group of 14 patients under 30 years of age who were treated before December 1939, all of whom had toxic symptoms. Six were definitely toxic, and the organism cultured from the blood in each instance was a very potent toxin producer. These 6 patients all died within nine days of onset of the illness. Five others had mild to moderately toxic symptoms, but severe persistent infection was superimposed on these patients, who were already weakened by the toxin, and all 5 succumbed. Three children of the entire group survived. One had symptoms of moderate toxicity, and the offending staphylococcus produced a potent toxin. This patient received fair amounts of antitoxin and survived. The other 2 children had symptoms of mild toxicity, their infections were controlled and they survived. Many therapeutic modalities were employed for these 14 patients, the most frequent being bacteriophage, the then known sulfonamide compounds, and staphylococcus antitoxin. There were instances in which a temporary response to antitoxin occurred, but, in the light of our present knowledge, the serum was improperly given and in inadequate dosage, and we do not believe that death in these instances can properly be attributed to failure of the antitoxin. The other medications showed no promise at all.

SUMMARY

Certain strains of staphylococci will produce a potent exotoxin under special in vitro conditions.

This exotoxin when injected intravenously into experimental animals causes a characteristic response ending in the death of the animal.

Toxigenic staphylococci when injected intravenously into experimental animals are capable of producing exotoxin in vivo with the resultant characteristic response.

Systemic infection by toxigenic staphylococci in human beings who are susceptible to the toxin is associated with clinical symptoms which are characteristic and readily recognizable.

This exotoxin can be neutralized in vivo by commercial staphylococcus antitoxin, which produces dramatic and life-saving results when properly administered. The use of staphylococcus antitoxin in certain cases exhibiting the characteristic features of staphylococcic toxemia is recommended as a valuable adjunct in their therapeutic management.

The members of the attending staff and the house staff of the Hospital for Joint Diseases and Drs. Charles Wise and Henry M. Kaessler, of the Mount Vernon Hospital, Mount Vernon, N. Y., cooperated in the work reported in this article.

Madison Avenue and One Hundred and Twenty-Third Street.

TRIGEMINAL NEURALGIA DUE TO RADICULAR LESIONS

WALLACE B. HAMBY, M.D.
BUFFALO

The partial section of the trigeminal sensory root by the temporal approach, as perfected by Spiller and Frazier from the Hartley-Krause operation for the relief of trigeminal neuralgia, has been acclaimed the most perfect operation known to surgery. A certain degree of morbidity indicates that this perfection is only relative. In search of a better treatment for this disease, Dandy [1] in 1925 began cutting the sensory root near the pons by the subcerebellar approach. While this operation has improved some morbidity rates, it has not eliminated them. Because the depth and location of the point of rhizotomy expose other nerve roots and important blood vessels to operative trauma, the majority of neurosurgeons have not discarded Frazier's operation in its favor.

One of the important by-products in the development of the suboccipital approach was the disclosure of a previously unrecognized frequency of gross etiologic lesions. In the first 200 cases in which this operation was used, Dandy [2] found that in 10 cases (5 per cent) a tumor of the cerebellopontile angle was responsible for the condition. In another series,[3] of 250 cases, he found 18 tumors of the cerebellopontile angle. In 1939 [4] he stated that in 5 per cent of cases the pain is due to a tumor, in another 5 per cent of cases to an aneurysm of the basilar artery and "in nearly all others" to a vascular anomaly causing pressure on the sensory root. In 1941 [5] he found "approximately 10 per cent" of cases of trigeminal neuralgia caused by a tumor in the cerebellopontile angle. Hyndman, who also employs the subcerebellar approach frequently, stated [6] that he had not yet found a tumor responsible for the pain, but [7] that if there exists the slightest doubt of the possibility of a tumor of the cerebellopontile angle, the cerebellar approach is the one of choice. He expressed the opinion that such a lesion should betray its presence by at least a diminution of the corneal reflex.

THE LOCATION OF LESIONS PRODUCING TRIGEMINAL PAIN

Authors have expressed various opinions as to the cause and site of origin of the pain of trigeminal neuralgia. It is the general consensus that an organic lesion

---

From the University of Buffalo School of Medicine and the Buffalo General Hospital.
Read before the American Academy of Neurological Surgery, Chicago, Oct. 17, 1942.

1. Dandy, W. E.: Section of Sensory Root of Trigeminal Nerve at the Pons, Bull. Johns Hopkins Hosp. **36**:105-106 (Feb.) 1925.

2. Dandy, W. E.: Lesions of the Cranial Nerves, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Co., Inc., 1932, vol. 12, chap. 1.

3. Dandy, W. E.: Treatment of Trigeminal Neuralgia by Cerebellar Route, Ann. Surg. **96**:787-795 (Oct.) 1932.

4. Dandy, W. E.: Lesions of Cranial Nerves: Diagnosis and Treatment, J. Internat. Coll. Surgeons **2**:5-13 (Jan.-April) 1939.

5. Dandy, W. E.: Results of Removal of Acoustic Tumors by Unilateral Approach, Arch. Surg. **42**:1026-1033 (June) 1941.

6. Hyndman, O. R.: Personal communication to the author.

7. Hyndman, O. R.: Tic Douloureux: Partial Section of Root of Fifth Cranial Nerve: Comparison of Subtemporal and Cerebellar Approaches from Surgical and Physiologic Standpoints, Arch. Surg. **37**:74-99 (July) 1938.

of the trigeminal pathways produces pain associated with sensory changes and not easily mistaken for major trigeminal neuralgia. The literature affords ample evidence that this is not always true and that a lesion affecting the trigeminal system in one of several places may produce pain indistinguishable from that of tic douloureux.

Peripheral Branch of Nerve or Gasserian Ganglion.—Dandy [4] stated that while pressure on the sensory root may produce trigeminal neuralgia, pressure on a peripheral branch of the nerve or the gasserian ganglion can never produce paroxysmal pain. This type of pain always means pressure on the root between the ganglion and the brain stem. Frazier [8] reported a case of a meningioma involving the dura over the ganglion, producing "jumpy" pain "like tic" but with a background of steady pain and with numbness of the lip. Cushing [9] said that while a tumor of the middle fossa compressing the gasserian ganglion may cause trigeminal pain, it usually is not like tic, being more continuous and accompanied by sensory loss. Peet [10] reported 2 cases of tumor of the antrum invading the maxillary nerve and ganglion, not affecting the sensory root. The patients had ticlike pain but with a background of pain, burning and numbness of the face. Mixter and Lund [11] reported a case of malignant neurogenic (?) tumor progressing along the maxillary nerve into the ganglion, also producing "lancinating pain" and sensory loss. On the other hand, Hyslop [12] reported a case of osteoma of the middle fossa compressing the first and second divisions of the trigeminal nerve near their foramens of exit. The patient had suffered tic for eighteen years and had received the usual relief from injection of alcohol. The pain was relieved by removal of the osteoma, the sensory root not being severed. Love and Woltman [13] reported 2 cases of tumor of the cavum Mecklii producing tic douloureux. One growth was an epidermoid among the posterior rootlets; the other, a meningioma beneath the root and ganglion. One patient was not entirely free of discomfort between paroxysms; otherwise the clinical picture in both cases was typical of trigeminal neuralgia. These were the only unsuspected tumors disclosed by rhizotomy for tic douloureux. I [14] have recently seen a patient whose sole complaint was typical tic in the distribution of the second division, caused by an aneurysm of the internal carotid artery within the cavernous sinus. The peripheral branch (maxillary) and possibly the ganglion were compressed by the lesion. Glaser [15] considered the ganglion the site of origin of tic pain. In general, while organic involvement of the ganglion and a peripheral branch of the nerve produces pain and sensory loss that are characteristic, the syndrome may not be complete and may pass for trigeminal neuralgia.

---

8. Frazier, C. H.: An Operable Tumor Involving the Gasserian Ganglion, Am. J. M. Sc. **156**:483-490 (Oct.) 1918.

9. Cushing, H.: Major Trigeminal Neuralgias and Their Surgical Treatment Based on Experiences with Three Hundred and Twenty-Two Gasserian Operations: Varieties of Facial Neuralgias, Am. J. M. Sc. **160**:157-184 (Aug.) 1920.

10. Peet, M. M.: Tumors of Gasserian Ganglion, with Report of Two Cases of Extracranial Carcinoma Infiltrating the Ganglion by Direct Extension Then Maxillary Division, Surg., Gynec. & Obst. **44**:202-207 (Feb.) 1927.

11. Mixter, W. J., and Lund, C. C.: Tumor of the Gasserian Ganglion: Report of a Case, Arch. Neurol. & Psychiat. **35**:432-433 (Feb.) 1936.

12. Hyslop, G. H.: Face Pain, New York State J. Med. **36**:91-95 (Jan. 15) 1936; personal communication to the author.

13. Love, J. G., and Woltman, H. W.: Trigeminal Neuralgia and Tumor of the Gasserian Ganglion, Proc. Staff Meet., Mayo Clin. **17**:490-496 (Sept. 9) 1942.

14. Hamby, W. B.: Trigeminal Neuralgia Due to a Subclinoid Aneurysm of the Internal Carotid Artery, Neurosurg. Ward Rounds **3**:1 (Oct.) 1941.

15. Glaser, M. A.: Tumors Arising from Sensory Root of Trigeminal Nerve in Posterior Fossa: Perineurial Fibroblastoma, Ann. Surg. **101**:146-155 (Jan.) 1935.

Sensory Root.—In his monograph "Tumors of the Nervus Acusticus," Cushing [16] stated that these tumors produce neuralgic pain relatively infrequently and that none of his patients presented pain characteristic of tic douloureux. He mentioned a case of cholesteatoma reported by Krause,[17] a case of meningioma (?) reported by Lexer [18] and a case of sarcoma reported by Weisenburg,[19] in each of which the tumor had produced ticlike pain. He emphasized the point that paralytic rather than irritative trigeminal phenomena predominate with tumors of the cerebellopontile angle. Glaser,[15] in reporting a case of primary perineurial fibroblastoma of the trigeminal sensory root, found no ticlike pain and attributed its absence to the fact that the gasserian ganglion was not involved. Dandy [20] reported a case of tic due to a small acoustic neurinoma and said [3] that the tic so produced is clinically indistinguishable from that not due to a tumor. Parker [21] reported 2 cases of tic due to an acoustic tumor. In 5 cases of tic with gross etiologic lesions, Raney and Raney [22] found adhesions of the sensory root in the temporal region (cases 1 and 4) and compression of the root in the cerebellopontile angle by varices (case 2) and acoustic neurinomas (cases 3 and 5). In Weisenburg's case [19] both trigeminal and glossopharyngeal neuralgia were produced by a "sarcoma" of the cerebellopontile angle.

Central Sensory Pathways.—In a discussion of trigeminal neuralgia accompanying multiple sclerosis, Finesilver [23] stated that he was unable to come to a conclusion as to the location of the lesion producing trigeminal pain. He mentioned 3 cases in which the pain was relieved by section of the root and injection of alcohol but could not explain the fact that it was relieved by maneuvers that were peripheral to its probable origin. Frazier, Lewy and Rowe [24] concluded that trigeminal neuralgia, and eventually other forms of typical neuralgia, represent special forms of the thalamic syndrome. In 1 case of typical thalamic pain, they relieved the facial pain by injection of alcohol into the trigeminal nerve and the pain in the body by cordotomy. This suggested to them that thalamic pain can be relieved by abolishing afferent impulses to the thalamus. In postmortem studies on patients who had had trigeminal neuralgia, Lewy and Grant [25] found degeneration of the internal and lateral thalamic nuclei bilaterally, with loss of white matter and widening of the ventricles. In 5 patients with unilateral lesions the softening was on the side of the pain. Lewy and Grant offered evidence that these lesions were caused by functional or organic vascular insufficiency.

---

16. Cushing, H.: Tumors of the Nervus Acusticus, Philadelphia, W. B. Saunders Company, 1917, pp. 163.

17. Krause, F.: Operationen in der hinteren Schädelgrube, Arch. f. klin. Chir. **81**:40-60, 1906.

18. Lexer, E.: Zur Operation des Ganglion Gasseri nach Erfahrungen an 15 Fällen, Arch. f. klin. Chir. **65**:843-928, 1902.

19. Weisenburg, T. H.: Cerebello-pontile Tumor Diagnosed for Six Years as Tic Douloureux: Symptoms of Irritation of the Ninth and Tenth Cranial Nerves, J. A. M. A. **54**:1600-1604 (May 14) 1910.

20. Dandy, W. E.: Operations for Cure of Tic Douloureux: Partial Section of Sensory Roots at Pons, Arch. Surg. **18**:687-734 (Feb.) 1929.

21. Parker, H. L.: Paroxysmal Trigeminal Pain with Tumors of the Nervus Acusticus, J. Neurol. & Psychopath. **17**:256-261 (Jan.) 1937.

22. Raney, R. B., and Raney, A. A.: Trigeminal Neuralgia with Gross Causative Lesions: Report of Five Cases, Am. J. Surg. **50**:227-238 (Nov.) 1940.

23. Finesilver, B.: Trigeminal Neuralgia in Multiple Sclerosis, J. Nerv. & Ment. Dis. **90**: 757-764 (Dec.) 1939.

24. Frazier, C. H.; Lewy, F. H., and Rowe, S. N.: Origin and Mechanism of Paroxysmal Neuralgic Pain and Surgical Treatment of Central Pain, Brain **60**:44-51 (March) 1937.

25. Lewy, F. H., and Grant, F. C.: Physiopathologic and Pathoanatomic Aspects of Major Trigeminal Neuralgia, Arch. Neurol. & Psychiat. **40**:1126-1134 (Dec.) 1938.

PERSONAL EXPERIENCES

Probably as the result of training, I prefer to use the temporal approach to the root in uncomplicated cases of tic douloureux. The cerebellar approach has been employed in only 9 cases in a series of 109 operations for trigeminal neuralgia, although it was used in an additional 10 cases in which some other sensory root was severed for relief of pain due to a malignant tumor. In 2 of the 9 cases, a "pearly tumor" (epidermoid) of the cerebellopontile angle was found. The cerebellar approach was chosen in 1 of the 9 cases because of minimal symptoms suggestive of such a tumor, in another because the pain followed (four and one-half years) the previous removal of a meningioma of the cerebellopontile angle and in 2 others because a previous unsuccessful temporal operation on the sensory root or a peripheral branch of the nerve had so distorted findings that the possibility of a tumor could not be excluded clinically.

REPORT OF CASES

CASE 1.—*Patient of 31 years with typical third division tic douloureux of six months' duration, with occasional "dizziness"; injection of alcohol into third division of trigeminal nerve, followed by imperfect relief and by slight homolateral facial paresis; suboccipital approach to sensory root, disclosure and removal of epidermoid of cerebellopontile angle; relief.*

Mrs. M. D., aged 31, was referred by Dr. W. J. Tracy, of Hornell, N. Y., on Jan. 20, 1936. In July 1935 she had experienced her first attack of paroxysmal, instantaneous pain in the right side of the lower jaw radiating anterior to the ear. Talking and laughing initiated attacks, but no history of an external "trigger zone" was obtained. In November the attacks became more frequent and often followed one another closely. In December her teeth were extracted, but no relief resulted. She admitted occasional "dizziness," although no history of vertigo was obtained. The neurologic examination revealed no abnormalities. Alcohol was injected into the third division of the trigeminal nerve, producing anesthesia and relief of pain.

On Feb. 11, 1936, the patient was admitted to the Buffalo General Hospital. The paroxysmal attacks of pain had ceased, but the jaw still was "sore." At that time there was a question of very slight weakness in the lower part of the face on the right side. Because of the history of slight dizziness and the questionable facial paresis, it was decided to approach the root posteriorly through the cerebellopontile angle rather than through the temporal fossa.

On Feb. 12, 1936, this approach was made with the patient under anesthesia induced with avertin with amylene hydrate and in the sitting position (fig. 1). The seventh and eighth cranial nerves were found normal. Just anterior to them was seen the tip of a typical "pearly tumor" (epidermoid). Its very thin capsule was opened, and the flocculent content was removed. The mass extended anterior to and beneath the fifth nerve, which was displaced backward. Its size was estimated to be 12 by 24 mm., its long axis being in the sagittal plane. At the completion of the procedure the fifth nerve was free in its course and so was not severed. The usual closure was made.

A letter written on May 4, 1938 stated that the patient was free of symptoms.

CASE 2.—*Woman of 41 years with typical second and third division tic douloureux for four years; three injections of alcohol, each followed by relief for decreasing periods; temporal section of sensory root planned; on morning of operation, first attack of vertigo, tinnitus and emesis with nystagmus and diminished corneal reflex for first time; exploration of cerebellopontile angle; removal of epidermoid; partial section of sensory root; relief.*

Mrs. M. P., aged 41, was referred to the Buffalo General Hospital by Dr. Robert Tuttle, of Gowanda, N. Y., on Dec. 26, 1940. For four years she had suffered attacks of typical trigeminal neuralgia in the areas of distribution of the second and third divisions of the left fifth nerve. Two years before, alcohol had been injected by a dentist into the third division. There was relief of pain for twenty-one months. A second injection gave relief for four months, and a third, no relief at all.

The neurologic examination gave entirely normal results except for revealing typical "trigger zones" in the upper and lower lips. The patient was scheduled for temporal sensory rhizotomy on the following day.

On the morning of operation, she awakened feeling dizzy, complained of tinnitus on the left side and vomited. Examination revealed nystagmus on looking to either side and diminution of the left corneal reflex. The remainder of the neurologic examination gave negative results. Because of this series of events, it was decided to explore the cerebellopontile angle and to do a partial rhizotomy if no lesion was found.

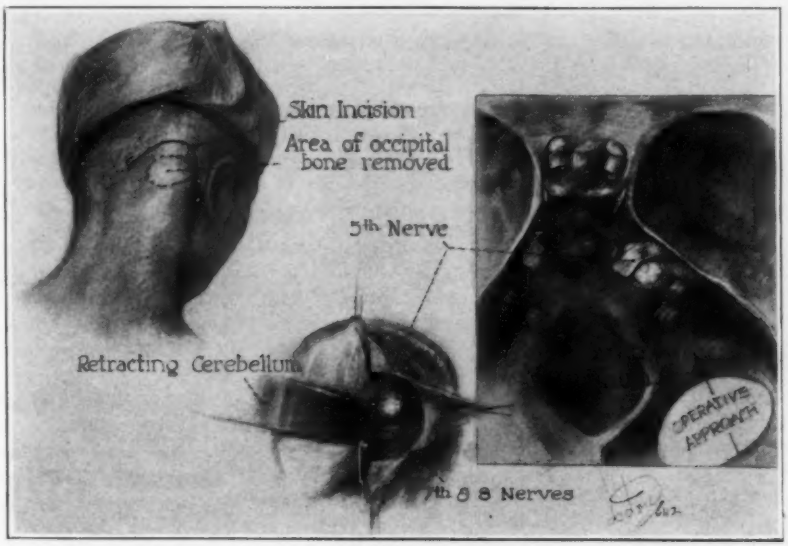


Fig. 1 (case 1).—Small epidermoid ("pearly tumor") under sensory root of trigeminal nerve, producing tic douloureux.

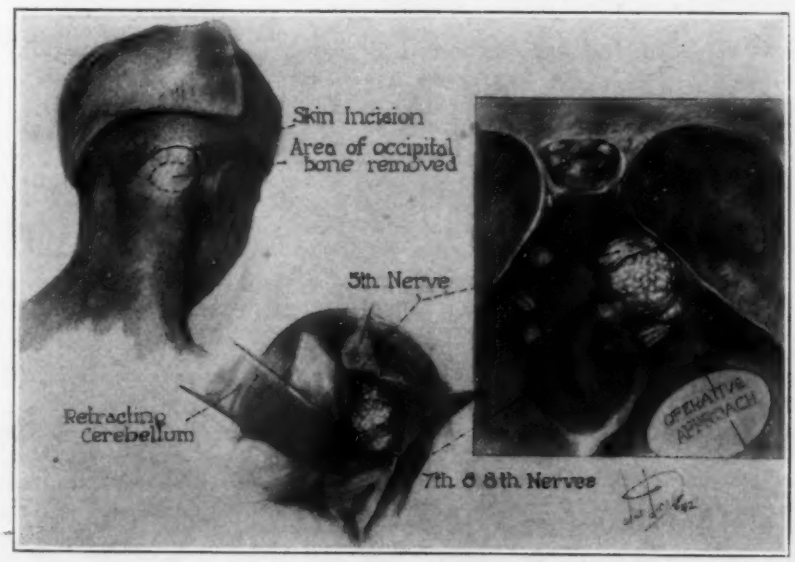


Fig. 2 (case 2).—Epidermoid ("pearly tumor") under sensory root of trigeminal nerve and facial and acoustic nerves, producing tic douloureux.

On December 27, with the patient under anesthesia induced with pentothal sodium (given intravenously) and in the sitting position, the left cerebellopontile angle was explored (fig. 2). At the level of the jugular foramen, a typical "pearly tumor" (epidermoid) 8 mm. in diameter was exposed. This was removed, and as its anterior end was reached it was found to be

attached to a much larger mass in the cerebellopontile angle. It was lobulated, and most of it lay behind the seventh and eighth nerves but a rather large mass extended anterior to the fifth nerve. After the soft contents had been evacuated, the capsule was teased out as completely as possible. The fifth, seventh and eighth nerves had been elongated by traction. The lower half of the fifth nerve was cut to prevent recurrence of pain. The usual closure was made.

Postoperatively, analgesia was present in the domain of the second and third divisions of the fifth nerve and the mild paresis of the lower part of the face persisted. The patient was discharged on Jan. 8, 1941.

CASE 3.—*Woman of 60 years with syndrome of tumor of right cerebellopontile angle; removal of meningioma of internal acoustic meatus; relief, two years later, short period of tic douloureux on left side, which subsided; four and one-half years later, onset of tic on right side; findings suggested recurrence of neoplasm; exploration revealed only arachnoid adhesions involving trigeminal sensory root; partial section of root; relief.*

Mrs. A. V., aged 60, was seen in consultation with Dr. C. W. Streets, of Fort Erie, Ontario, Canada, on Feb. 14, 1935. She had suffered paroxysmal attacks of tinnitus on the right side for five years and had had gradual visual failure for one year. For one month she had noticed paroxysmal attacks of vertigo and vertex headaches. For ten days slight pain and numbness had affected an area about the right eye and the lower right front teeth and paresthesias had involved the right arm and hand.

Examination revealed opacity of both lenses and no papilledema. The corneal reflexes were intact. No nystagmus was found. Hypalgesia was present around the lateral end of the right supraorbital ridge and at the right angle of the mouth. No facial paresis was seen. Hearing by both air and bone conduction was diminished in the right ear. Caloric vestibular tests revealed a nonfunctioning right labyrinth. The extremities were not ataxic, but the patient fell forward on bending. Hyperesthesia was demonstrated on the dorsum of the right hand. A diagnosis of tumor of the right cerebellopontile angle was made.

The patient was admitted to the Buffalo General Hospital on Feb. 20, 1935. On the following day the right cerebellopontile angle was explored. The nerves entering the jugular foramen were normal. Growing from the internal acoustic meatus was a firm, friable, reddish gray ovoid tumor, 15 by 20 mm., extending upward and anteriorly. The capsule was collapsed by curettage of the contents, one large afferent artery being coagulated and severed. The seventh and eighth cranial nerves then were seen pushed forward by the mass and not grossly implicated in its growth. The tumor was adherent only to the dura at the posterior lip of the internal auditory meatus. The fifth nerve was seen farther forward and did not appear grossly involved. The capsule was excised cleanly, and its base was coagulated. The usual closure was made.

Pathologic examination revealed a typical meningioma. The patient's convalescence was complicated by an attack of cholelithiasis, from which she recovered. Except for deafness of the right ear the symptoms and signs referable to cranial nerves all subsided prior to her discharge, on March 13.

She returned on June 26, 1940. A cholecystectomy had been done three years before. In 1938 she had suffered for four months with typical attacks of tic douloureux on the left side, which had cleared completely. For the past eight months she had suffered typical attacks of tic on the right side. She felt somewhat dizzy, and since she was almost blind from progression of the cataracts, she could not walk well alone. Examination revealed opacity of both lenses that precluded inspection of the optic disks. Otherwise the eyes were normal. There was no paresis of facial motion or sensation. The right ear was deaf. The right side of the body was weaker than the left, and both hands were ataxic. The reflexes were hyperactive but were equal on the two sides. A recurrence of the neoplasm was suspected.

On June 30 the patient was readmitted to the Buffalo General Hospital, and on the following day the right cerebellopontile angle was again explored, by reopening the old incision. The seventh and eighth nerves were diminished in size, but there was no evidence of recurrence of the neoplasm. The sensory root of the fifth nerve was firmly enshrouded in arachnoid adhesions. This root was isolated, and the posterior two thirds was severed. The usual closure was made.

After the operation she was free of pain. The right side of the face was anesthetic except for the cornea, and there was some weakness of the left arm and leg that persisted until her discharge, on July 11.

CASE 4.[26]—*Woman of 48 years, with syndrome of a right acoustic neurinoma; severe third division trigeminal neuralgia on right side five years before; four years before, subtotal resection of sensory root, with complete relief; operation followed by tinnitus on right side for eight months and progressive deafness of right ear; two years before recurrence of pain in distribution of second division of right trigeminal nerve; peripheral neurectomy and injection of alcohol ineffectual; removal of acoustic neurinoma.*

Mrs. E. R. M., aged 48 years, was admitted to the Cleveland Clinic on Dec. 17, 1933. Five years before, she had suffered typical trigeminal neuralgia in the right side of the lower jaw. A year later a subtotal resection of the sensory root was done elsewhere. After the operation the patient noticed tinnitus and progressive deafness and pain in the right ear. Within eight months the deafness was complete and tinnitus ceased. Three years later, typical tic developed in the distribution of the second division of the right fifth nerve. Peripheral operations and injections resulted in painful anesthesia. For two years she had staggered occasionally in walking.

Examination revealed horizontal nystagmus on lateral gaze. The optic disks showed borderline edema. The visual fields were normal. Both corneal reflexes were absent. The skin of the face was anesthetic in the distribution of the third division of the right trigeminal nerve and was hyperesthetic painfully in the distribution of the second division. Taste was lost in the right half of the tongue. The jaw deviated to the right on opening. There was mild peripheral paresis of the right side of the face. The right ear was deaf, and the labyrinth did not respond to caloric stimulation. The tendon reflexes were exaggerated, without Babinski's sign. Romberg's sign was present mildly, and no other ataxia was found. A diagnosis of trigeminal neuralgia secondary to an acoustic tumor on the right side was made.

Intracapsular removal of an acoustic neurinoma was performed by Dr. Gardner on Dec. 18. The portion of the capsule that seemed to carry the seventh nerve was preserved. The fifth nerve could not be found and was believed to have been destroyed with the capsule. The patient recovered, and some sensation returned to the right side of the face.

COMMENT

In case 1 the findings suggestive of a tumor of the cerebellopontile angle were meager. The patient was 31 years old, younger than the average person suffering from trigeminal neuralgia, though Dandy[2] has reported the disease in a child of 15 and Klemme[27] in a boy of 10 years. Mild homolateral tinnitus and a mild facial weakness (which was apparent only after an injection of alcohol three weeks before) were the only other suggestive phenomena. In case 2 no suspicion of a neoplasm was entertained until on the morning of operation the patient complained of vertigo and displayed nystagmus and corneal hypesthesia for the first time since she had been under observation. Interestingly, both of these patients had obtained the usual amount of relief following injection of alcohol into the peripheral nerves. This phenomenon also was recorded by Abbott and Merkel.[28] Blocking afferent stimuli at times may relieve pain due to a lesion of the sensory root as well as that due to a central lesion, as suggested by Frazier.[8] Relief is not always obtained in this way. Weisenburg's[19] patient did not obtain relief after section of the sensory root; the pain may have been attributable to the glossopharyngeal involvement. In case 4 pain was relieved in the area denervated by section of the root but persisted in spite of peripheral operations in later affected areas.

---

26. The presentation of this case was made possible by Dr. W. James Gardner, of the Cleveland Clinic, Cleveland, Ohio. Brief reference has been made to it previously (Hamby, W. B.: Acoustic Neurinomas in the Stage of Normal Intracranial Pressure, New York State J. Med. **35**:1143-1147 [Nov. 15] 1935.

27. Klemme, R. M.: Accurate Subtotal Resection of Sensory Root for Relief of Major Trigeminal Neuralgia, South. M. J. **28**:1086-1091 (Dec.) 1935.

28. Abbott, W. D., and Merkel, B. M.: Acoustic Neuroma Producing Tic Douloureux. J. Iowa M. Soc. **30**:465-468 (Oct.) 1940.

A review was made of the records of 96 patients whose trigeminal neuralgia had been cured by temporal section of the sensory root in 100 operations. Findings suggestive of paralytic involvement of the trigeminal nerve or of involvement of neighboring nerve roots or of the cerebellum were absent. In 3 patients residual signs were found of a previous clinically diagnosed cerebral vascular accident, and in 1 evidence of combined sclerosis was noted.

A review was made of the records of 22 other patients in whom a tumor of the cerebellopontile angle or of the anterior portion of the cerebellar hemisphere was verified at operation. None of these patients had suffered pain suggestive of trigeminal neuralgia, although 9 of them had sufficient involvement of the sensory root to produce diminution of sensation in the face and 14 of them had diminished corneal reflexes. Minimal compression of the root in case 1 was followed by tic douloureux, while in other cases extensive stretching and displacement of the root by a huge tumor did not result in pain. Minimal involvement of the root probably is in itself not the cause of the pain. In case 3 a small meningioma which just touched the root did not produce pain, although typical tic developed four and one-half years later. At this time the sensory root was surrounded by arachnoid adhesions. In another patient with a small recurrence of a meningioma of the cerebellopontile angle around the sensory root, tic douloureux did not develop. Although the neoplasm responsible for the neuralgia in 2 instances here was an epidermoid, another huge epidermoid in my series did not produce the pain even though it distorted the sensory root severely.

CONCLUSIONS

Cases reported in the literature reveal that while a tumor compressing a peripheral branch or the ganglion of the trigeminal nerve may produce "ticlike" pain, this usually is secondary in importance to the steady background pain and the sensory loss that accompany it. Compression of the sensory root of the nerve by a tumor of the cerebellopontile angle may produce pain and sensory loss indistinguishable from symptoms caused by a tumor of the middle fossa, but involvement of the neighboring nerve roots usually permits differentiation.

A lesion affecting the trigeminal pathways in the temporal fossa or in the cerebellopontile angle may produce pain indistinguishable from that of major trigeminal neuralgia. Such lesions are more numerous in the posterior than in the middle fossa. In my small series, minimal signs of involvement of the adjacent nerves allowed the differentiation of location to be made, but in the second case this did not occur until the morning of operation. Obviously, if these telltale signs had occurred a few days later, the lesion would have been missed and the symptoms attributed to postoperative sequelae. Experience has shown that section of the sensory root by either approach will relieve trigeminal pain, whether it originates peripheral or central to the gasserian ganglion. Although review of the series of cases in which temporal trigeminal rhizotomy was performed showed that signs referable to the posterior fossa were not present at the time of study, some neoplasms of the cerebellopontile angle may go undisclosed to the grave with elderly patients, who presumably die of extraneous causes within a few years of operation. Dandy's large series proves that the association of these lesions is more than coincidental.

Although my limited experience bears out Dandy's greater one that section of the sensory root of the trigeminal nerve by suboccipital approach is safe and is

followed by little morbidity when done by modern neurologic surgeons, it is my impression that the temporal approach is preferable for the elderly, perhaps "poor risk" patient. To the group of persons suspected of having a tumor of the cerebellopontile angle, for whom the posterior approach is indicated, should be added the younger patients with trigeminal neuralgia. In substituting Sjöqvist's [29] trigeminal tractotomy for sensory rhizotomy in the treatment of trigeminal neuralgia, the same criteria in the selection of cases must be used; the cerebellopontile angle should not go unexplored when exploration is indicated. This is possible, since the operation is easily done through a midline incision that is simpler than the larger muscle flap operation.

SUMMARY

A tumor compressing a peripheral branch or the ganglion of the trigeminal nerve may produce "ticlike" pain that usually is accompanied by steady background pain, burning and numbness. The pain may pass for that of trigeminal neuralgia.

A tumor of the cerebellopontile angle compressing the sensory root may produce a pain syndrome indistinguishable from that of a tumor of the middle fossa, but symptoms from adjacent nerve roots usually aid differentiation.

A tumor of the cerebellopontile angle may produce pain indistinguishable from major trigeminal neuralgia. Differentiating signs will appear later, but they may be absent at the time of examination and operation.

Tic pain due to a lesion of either the middle or the posterior fossa is relieved by injection of alcohol or temporal section of the sensory root of the trigeminal nerve.

Patients with tic douloureux must be examined carefully for signs referable to a possible lesion of the posterior fossa. If any doubt exists, the rhizotomy should be done via the posterior fossa. Patients younger than the average with tic douloureux deserve the posterior approach.

The posterior approach is safe and results in little morbidity. The temporal approach, in the hands of those more familiar with it, remains the operation of choice for the elderly, "poor risk" patient.

When trigeminal tractotomy is used for relief of tic douloureux, the cerebellopontile angle must be explored in every case presenting any question of a gross etiologic lesion.

140 Linwood Avenue.

29. Sjöqvist, O.: Studies on Pain Conduction in the Trigeminal Nerve, Acta psychiat. et neurol., 1938, supp. 17, pp. 1-139.

BILIARY DYSKINESIA

ROLE PLAYED BY A REMNANT OF THE CYSTIC DUCT

HOWARD K. GRAY, M.D.*
AND
WENDELL S. SHARPE, M.D.
Fellow in Surgery, Mayo Foundation
ROCHESTER, MINN.

The problem of persistence of typical preoperative symptoms after cholecystectomy for supposed cholecystic disease is well known and extremely perplexing. Probably because their cause is not known, a voluminous literature containing many conflicting theories on the subject has appeared. The symptom complex has been given many names, best known of which are biliary dyskinesia,[1] biliary dyssynergia and postcholecystectomy syndrome.

The purpose of this study was to survey an obscure aspect of the problem, namely, the role played by a remnant of the cystic duct and the effect of its removal. The material was obtained from a review of 44 cases in which operation was performed at the Mayo Clinic in the years 1910 to 1940 inclusive because of persistence of symptoms after cholecystectomy. These are, of course, only a small proportion of the cases in which exploratory operation was performed for such symptoms in that period, but in each of these 44 cases the surgeon remarked on the presence of an enlarged remnant of cystic duct and removed it. In all but 2 of these cases the patients were carefully followed.

It has come to be generally agreed that cholecystectomy when performed with proper and adequate indication is a remarkably successful operation. If stones are present, permanent benefit is obtained in 80 to 95 per cent of cases, and only slightly less satisfactory are the results obtained by removal of noncalculous gallbladders in which there is evidence of advanced disease.[2] The presence of stones is evidence of disease, and in cases in which there is an adequate history of biliary distress cholecystectomy usually is indicated and offers a good prospect of permanent cure. Whipple[3] reported that the procedure failed to relieve symptoms in only 1.8 per cent of such cases. As the indications for cholecystectomy have become less rigid, less favorable results have been reported. It is undoubtedly true that erroneous diagnosis may unjustly indict the gallbladder and after its ill

* From the Division of Surgery, the Mayo Clinic.

1. Westphal, K.: Muskelfunction, Nervensystem und Pathologie der Gallenwege: I. Untersuchungen über den Schmerzanfall der Gallenwege und seine ausstrahlenden Reflexe, Ztschr. f. klin. Med. **96**:22-51, 1923; II. Experimentelle Untersuchungen über die nervöse Beeinflussung der Bewegungsvorgänge der Gallenwege, ibid. **96**:52-94, 1923; III. Die Motilitätsneurose der Gallenwege und ihrer Beziehungen zu deren Pathologie, zur Stauung, Entzündung, Steinbildung usw., ibid. **96**:95-150, 1923.

2. Dwyer, M. F., and Dowling, G. A.: Results in Cholecystectomy, with Special Reference to the Symptomatology and Diagnosis of Cholecystitis, J. A. M. A. **98**:722-726 (Feb. 27) 1932. Judd, E. S.: Clinical Versus Pathologic Cholecystitis, in Collected Papers of the Mayo Clinic and Mayo Foundation, Philadelphia, W. B. Saunders Company, 1925, vol. 17, pp. 152-156. Muller, G. P.: The Noncalculous Gallbladder, J. A. M. A. **89**:786-789 (Sept. 3) 1927.

3. Whipple, A. O.: Surgical Criteria for Cholecystectomy, Am. J. Surg. **40**:129-131 (June) 1926.

advised removal symptoms may persist in spite of the operation and not because of it. This is true in such a group of cases as those which constitute a portion of the present study, and, as will be shown, the majority of the patients have no striking symptoms of biliary distress and usually consult a physician because of vague indigestion.

CAUSES OF THE POSTCHOLECYSTECTOMY SYNDROME

The persistence of symptoms after cholecystectomy occurs too frequently to be disregarded. The largest contributing factor probably is erroneous diagnosis. It is often truly difficult to distinguish functional biliary distress from that of organic origin. Ill advised operation also is an etiologic factor. Weir and Snell [4] have said that the inflammatory or degenerative residua of cholecystic disease constitute a leading cause for the persistence of symptoms. Severe cholecystitis is usually accompanied by a certain amount of hepatitis, cholangitis and pancreatitis. Although the inflammatory reaction in the gallbladder may be sufficient to produce the typical distress, the residual inflammation of the biliary tract, if not resolved, may account for an unsatisfactory result. Stricture of the extrahepatic bile ducts may be another source of distress. It is relatively easy to injure them during cholecystectomy, and although complete stricture would result in jaundice or a biliary fistula, incomplete or partial stricture, with its attendant inflammatory reaction, may account for some instances of persistent distress. Residual stones or putty-like material in the common bile duct is a well known cause of recurrent colic and jaundice. Hill's [5] review of the literature, which emphasized the subject of reciprocal innervation of the musculature of the wall of the gallbladder and the sphincter of Oddi, opened the discussion of the cause of biliary colic. In some cases in which the patients are hyperirritable, obscure dyskinesia or dyssynergia of the ductile system, combined with malfunction of the sympathetic and parasympathetic nervous systems, may account for postcholecystectomy colic. Angulation of the duodenum by attachment to the denuded gallbladder fossa also may conceivably cause a certain amount of postoperative flatulence and vague epigastric distress. Last of all, Schmieden and Rhode [6] first called attention to the part played by lesions of the cystic duct in cholecystic disease. Cole and Rossiter [7] lately have reawakened interest in this phase of the problem. They listed the possible lesions responsible for obstruction of the cystic duct (table 1) and called attention to the fact that the fundus of the gallbladder at the time of cholecystectomy may appear entirely normal, just as in the reported cases of biliary dyskinesia, but the cystic duct may be obstructed, kinked or bound down by inflammatory reaction and be the cause of the distress. They said that acute inflammation of the cystic duct is a common occurrence and pointed to the presence of brawny edema, adhesions and even small abscesses about the cystic duct as evidence.

Cole and Rossiter reported 7 cases of cholecystic disease in which the symptoms were typical, but although at cholecystectomy the walls of the fundus of the gall-

4. Weir, J. F., and Snell, A. M.: Symptoms That Persist After Cholecystectomy: Their Nature and Probable Significance, J. A. M. A. **105**:1093-1098 (Oct. 5) 1935.

5. Hill, H. A.: Functional Disorders of the Extra-Hepatic Biliary System: Biliary Dyssynergia or Dyskinesia, Radiology **29**:261-278 (Sept.) 1937.

6. Schmieden, V., and Rhode, C.: Die Stauungsgallenblase mit besonderer Berücksichtigung der Ätiologie der Gallenstauungen, Arch. f. klin. Chir. **118**:14-53, 1921.

7. Cole, W. H., and Rossiter, L. J.: The Relationship of Lesions of the Cystic Duct to Gall Bladder Disease, Am. J. Digest. Dis. **5**:576-586 (Nov.) 1938.

bladder appeared essentially normal one or more of the lesions listed in table 1 were found in the region of the cystic duct. Cholecystectomy relieved the symptoms in all of these cases. Had the diseased cystic ducts not been recognized and removed, the patients may well have become "neurotic" and the so-called postcholecystectomy syndrome might have developed. This thought gave impetus to the present study.

Investigation of the anatomy involved demonstrated the possibility of such an oversight in surgical technic, because there is probably no portion of the body more subject to anomalies and wide variation than the gallbladder and its cystic duct. Operation in this region lends itself readily to the possibility of amputating the gallbladder above an anomalous cystic duct and leaving a good-sized stump which may dilate, remain inflamed or contain calculi. The cystic duct is usually about 3 mm. in diameter, that is, half the diameter of the hepatic duct, but it is 31 to 37 mm. in length. It begins at the neck of the gallbladder, which is curved medially toward the porta hepatis in the form of the letter "S." Around the interior of its cavity at this point are a series of crescentic folds, which are placed spirally and form the valvula spiralis of Heister. The cystic duct pursues a course

TABLE 1.—*Lesions Responsible for Obstruction (Partial or Temporarily Complete) of the Cystic Duct* *

1.	Stenosis produced by surrounding adhesions
2.	Stenosis produced by a thickened wall
	a. Owing to acute inflammation
	b. Owing to diffuse fibrosis
3.	Congenital or inflammatory twists or kinks
4.	Congenital or inflammatory lesions of the valves of Heister
	a. Fibrous strands
	b. Local deposition (nodules) of fibrous tissue
	c. Stricture caused by scar
	d. Valvelike anomalies
5.	Stone in the duct
6.	Tension induced by enlarged liver
7.	Compression or filling defect caused by tumor or lymph nodes
8.	Anomalous hepatic or cystic artery

* As determined by Cole and Rossiter.[7]

backward and medially to join the hepatic duct and form the common bile duct. There are many variations in this course and many irregularities in the shape, situation and size of the cystic duct.

In our study it soon became apparent that the 44 cases could be divided into two well defined groups. The first group includes 18 cases in which calculi were found in the common bile duct or in the stump of the cystic duct when operation was performed to relieve the persistent distress which occurred after cholecystectomy. In 11 of the 18 cases the calculi were found in the common bile duct, and in 7 the calculi were found in the stump of the cystic duct (table 2). The second group includes 26 cases in which no calculi were found at the second operation. The enlarged remnant of the cystic duct was removed in all of the 44 cases (table 2).

GROUP 1

In the 18 cases which comprise this group, 13 of the patients were women and 5 were men. When the operations were performed for the relief of the persistent distress, the ages of the patients ranged from 24 to 66 years. In 16, or 89 per cent, of the cases which comprise this group, definite gallbladder colic had been present before the primary operation on the biliary tract was performed. The colic had been associated with severe attacks of nausea and vomiting and residual sore-

TABLE 2.—*Clinical and Pathologic Observations and Treatment*

	Cases		Symptoms of Cholecystic Disease Before Cholecystectomy		Cholelithiasis Found at Cholecystectomy	Appearance of Persistent Symptoms After Cholecystectomy		Subsequent Operation: Pathologic Observations					Subsequent Operation: Operative Procedure		Results Based on Follow-Up Data in 40 of 44 Cases
									Inflammation of Stump of Cystic Duct						
	Number	Per Cent	Characteristic	Mild or Absent		Early	Late	Hepatitis and Pancreatitis	Subacute	Acute	Chronic	Duodenum Adherent to Gallbladder Fossa	Removal of Stump of Cystic Duct and of Calculi When Present	Drainage of Common Bile Duct	
Group 1:															
Stone in common bile duct *	11	25	9	2	9	9	2	4	4	5	2	11	11	11	(Follow-up data in 10 cases); complete relief in 6 cases; no relief in 4 cases, including the 2 in which symptoms were mild or absent
Stone in stump of cystic duct *	7	16	7	0	6	1	6	1	5	..	2	7	7	6	(Follow-up data in 6 cases); complete relief in 5 cases; no relief in 1 case; 1 patient died seven years later
Group 2:															
Calculi not present *	26	59	19	7	19	16	10	11	5	16	5	26	26	22	(Follow-up data in 24 cases); complete relief in 11 cases; no relief in the 7 cases in which symptoms were mild or absent
Total	44	100	35	9	34	26	18	16	14	21	9	44	44	39	

* When operation was performed for the relief of symptoms that persisted after cholecystectomy.

ness had occurred in the right upper quadrant of the abdomen. In 3 of these cases the patients had had repeated attacks of chills and fever, and in 2 of the 16 cases jaundice had been noticed on at least one occasion. In 15, or 83 per cent, of the cases in this group, cholecystography had demonstrated the presence of calculi. In the 2 remaining cases, the patient had not had symptoms that were characteristic of cholecystic disease, but in 1 of them roentgenologic examination had disclosed cholelithiasis. In 1 of the 2 cases the patient had complained of vague, mild, rather constant indigestion, but in the other, in which stones were demonstrable roentgenologically, the patient had not had any symptoms. Cholecystectomy was warranted in at least 16 of the 18 cases. If the presence of biliary calculi is sufficient indication for cholecystectomy, the operation was indicated in all but 1 of these cases.

In 2 of the 18 cases, cholecystostomy had been performed several years before the patients were subjected to cholecystectomy. In the remaining 16, cholecystectomy was the primary operative procedure. In the 11 cases in which a subsequent operation disclosed a stone in the common bile duct, the interval between cholecystectomy and the appearance of the persistent postoperative distress was less than one month in 9 cases and two to five years in 2. Jaundice occurred in only 5 of these cases, but severe pain occurred in all. In these 11 cases, choledochostomy was performed and the enlarged stump of the cystic duct was removed. Microscopic examination disclosed subacute or acute inflammation of the stump of the cystic duct in 9 of the 11 cases. The presence of a stone in the common bile duct probably is sufficient to explain the persistent symptoms, but the active inflammation of the stump of the cystic duct is significant.

As stated previously, in 7 of the cases in group 1 a stone was found in the stump of the cystic duct when an operation was performed for the relief of the distress which occurred after cholecystectomy. The distress occurred immediately after cholecystectomy in only 1 of the 7 cases. In the remaining 6 cases the patients felt greatly relieved for sixteen months to nine years after cholecystectomy had been performed. The history was suggestive of biliary colic in only 1 case. In the other cases the patients complained of soreness in the region of the gallbladder, mild epigastric distress and occasional nausea and vomiting. In 5 of these 7 cases, the stump of the cystic duct not only contained a stone but also was subacutely inflamed. In 6 of the 7 cases, the common bile duct was explored at the time of the subsequent operation.

In all of the 18 cases in group 1 the duodenum was adherent to the gallbladder fossa. The operative notes did not mention severe angulation of the duodenum.

In 10 of the 11 cases in which a stone was found in the common bile duct, a careful effort was made to obtain follow-up data. The subsequent operation relieved the persistent distress in only 6, or 60 per cent. Cholecystectomy had been indicated in all 6. In the 2 cases in which the indications for cholecystectomy may be subject to question, the subsequent operation failed to relieve the persistent distress, although a stone was removed from the common bile duct.

In 2 of the 4 cases in which the subsequent operation failed to relieve the persistent distress, the patients returned to the clinic on several occasions and complained of "the same old distress and pain" for which "everything that had been tried" had failed. In 2 of these cases, other operations have been performed. In 1 of these choledochoduodenostomy was performed within a year after cholecystectomy for relief of the distress. Seven years after the last operation the patient still complained of attacks of nausea and vomiting, vague epigastric distress and dyspepsia. In the other case, an exploratory operation was performed ten months after the first operation for the relief of the distress that occurred after cholecys-

tectomy. No calculi were found at operation. A T tube was left in the common bile duct for a long time. The distress continued, and within two months the common bile duct was explored again. Four years after the last operation the patient was having attacks of bloating and distress about twice a month.

In 1 of the 7 cases in which operation for the persistent distress disclosed a stone in the stump of the cystic duct, the patient died of cardiac failure seven years later, and we were unable to obtain any information about the results of the operation. Follow-up data are available in the remaining 6 cases. The results were satisfactory in 5, or 83.3 per cent. In 4 the persistent distress disappeared after the operation and the patients were in good health when last heard from. In 1 of the 6 cases the patient has had at least two attacks of nausea, vomiting and severe indigestion which were similar to those she had experienced before the last operation.

Analysis of the results obtained in the cases in group 1 revealed one outstanding fact, namely, that the subsequent operation relieved the persistent distress in a large proportion of cases in which the indications for cholecystectomy appear to have been adequate.

GROUP 2

In the 26 cases which comprise this group, 20 of the patients were women and 6 were men. When the operations were performed for the relief of the persistent distress, the ages of the patients ranged from 25 to 66 years. For several years before cholecystectomy had been performed, the patients had had symptoms which had been ascribed to disease of the biliary tract. In 5 of the cases the patient had been subjected to cholecystostomy before cholecystectomy was performed.

In the 19 cases in which stones were found in the common bile duct, in the remnant of its cystic duct, the past history indicated that the patient had had cholecystic disease before cholecystectomy was performed and the operation appears to have been indicated. All of the 19 patients had had typical attacks of indigestion, which had been accompanied by nausea and vomiting, and 10 had had pain in the right upper quadrant of the abdomen, which had been severe enough to require medication. In 4 of the cases jaundice had followed one of the attacks and in 2 the patients had had attacks of chills and fever. In all of the 19 cases, calculi were found in the gallbladder when cholecystectomy was performed. In 7 of the 26 cases in the group, the patients had had few symptoms which would suggest sufficient disease in the gallbladder to indicate cholecystectomy. The symptoms had not been severe in any of these cases, and in most of them the distress had been minimal. Cholecystography had failed to reveal any calculi, and none were found when cholecystectomy was performed. Colic, jaundice, chills or fever had not occurred. The most frequent symptoms had been dyspepsia, pyrosis and constipation, and these had been noted for several years. It is probable that the diagnosis of cholecystic disease was erroneous and that the postoperative distress occurred in spite of, and not because of, cholecystectomy.

In 5 of the 7 cases in which calculi were not found in the gallbladder, the symptoms recurred immediately after cholecystectomy was performed, that is, before the patients were dismissed from the hospital. In 11 of the 19 cases in which calculi were found in the gallbladder, the symptoms recurred soon after cholecystectomy was performed. The symptoms were similar to those which had occurred before operation. However, colic occurred in fewer cases than it had before operation. Jaundice was said to have occurred in 2 cases, but this could not be verified. The most frequent symptoms were persistent soreness in the right upper quadrant of the abdomen, bloating, dyspepsia, flatulence, pyrosis and constipation. Vague

and atypical pain, which was present more or less constantly in the right upper quadrant of the abdomen, was almost a constant feature.

In all of the cases in this group, subsequent operation disclosed enlargement of the stump of the cystic duct. Microscopic examination of the sections of the stump disclosed subacute inflammation in 5 cases, acute inflammation in 16 and chronic inflammation in five (table 2). Although the common bile duct was enlarged in all of the cases, the enlargement was no greater than that usually observed after cholecystectomy. Mild pancreatitis or hepatitis or both was observed in 11 of the 26 cases in this group. No severe inflammation of the pancreas, liver or bile ducts was observed. In all of the cases the duodenum was adherent to the gallbladder fossa, but severe angulation was not noted. In a few cases the surgeon expressed the opinion that this mild distortion of the duodenum was sufficient to produce symptoms.

In analyzing the results of subsequent operation in this group of cases, the most striking feature was the condition of the patients in the 7 cases in which the indications for cholecystectomy may be subject to question. Although one to seventeen years had elapsed since operation was performed for the relief of the distress that had occurred after cholecystectomy, the patients still complained of the "same old distress" and 6 requested that further surgical procedures be employed. The other patient induced another surgeon to perform an exploratory laparotomy for "adhesions" three years after the stump of the cystic duct had been removed at the clinic. Since the last operation, she has been seen repeatedly at the clinic, and the persistent distress is still present after twelve years.

In the remaining 19 cases in this group, the indications for cholecystectomy appear to have been adequate. Follow-up data are available in 17. In 11, or 64.7 per cent, the subsequent operation relieved the distress. In 6, or 35.3 per cent, the distress was still present when the patients were last seen at the clinic.

COMMENT

Follow-up data were available in 40 of the 44 cases in this series. In 31 of the 40 cases, the indications for cholecystectomy may be said to have been adequate. In 22, or 70.9 per cent, of the 31 cases, the persistent distress was relieved by a subsequent operation which consisted of removal of the stump of the cystic duct and removal of calculi when found in the common bile duct or in the stump of the cystic duct. A subsequent operation failed to relieve the distress in all of the 9 cases in which the indications for cholecystectomy may be subject to question. Considering the entire group, about half of the patients were relieved by the subsequent operation.

SUMMARY AND CONCLUSIONS

Biliary dyskinesia, regardless of its cause, is a distressing problem. The two most probable causes of its occurrence are (1) erroneous diagnosis of cholecystitis and ill advised removal of the gallbladder with the persistence of some functional disorder of the choledochus sphincter and (2) residual inflammatory disease of the liver, pancreas or ductile system. The possibility that some inflammatory or mechanical lesion of the cystic duct may cause typical symptoms of cholecystic disease suggests that a similar lesion in a remnant of cystic duct may be the obscure cause of persistent pain after cholecystectomy. In many cases the removal of this remnant of cystic duct has been coincident with choledochostomy and choledocholithotomy. If the original operation was performed on the basis of adequate historical or roentgenographic indications or both, about 70 per cent of the patients

have been found to obtain relief of persistent symptoms by the second operation in which the cystic duct with or without stones is removed.

In this series of 44 cases all specimens of cystic duct removed showed evidence of disease; in 35 cases (79 per cent) there was evidence of recent inflammation.

In a series of 26 cases of biliary dyskinesia in which at the second operation only an enlarged inflamed remnant of cystic duct was incriminated and removed, approximately 65 per cent of the patients were relieved of their symptoms, provided that the first operation was well advised and necessary. If the first operation was performed on the basis of inadequate indications, 100 per cent failure resulted from the secondary operations in which only draniage of the common bile duct or removal of a remnant of cystic duct could be accomplished.

Too great stress cannot be placed on the importance of operating only in those cases in which there is definite and conclusive clinical or roentgenographic evidence of disease of the biliary tract. At the time of operation, meticulous care must be exercised in order to avoid damage to the common bile duct but at the same time all but a very small remnant of the cystic duct should be resected. In those cases in which the patient unfortunately experiences persistence or recurrence of pain after cholecystectomy and in which reoperation is deemed necessary, diligent search should be made for a remnant of the hepatic duct whether or not calculi are suspected in the common bile duct.

The Mayo Clinic.

RETICULOCYTOSIS FOLLOWING ABLATION OF FRONTAL CEREBRAL CORTEX

FRED A. METTLER, M.D., PH.D.
NEW YORK

In the course of studies on the evidences of autonomic imbalance which follow removal of cerebral cortex,[1] it has been possible to show that some of these effects are specifically due to frontal injury. One of these, as indicated in a preliminary report,[1f] and the easiest to follow is reticulocytosis. The present investigation is concerned with the latency and degree of this response of the blood as engendered by a frontal lesion.

EXPERIMENTS

Adult dogs which had been examined for freedom from parasites were placed on a standard diet and, after a preliminary observation period of thirty days during which the weight and reticulocyte count were frequently checked to ascertain that stability was being maintained, were subjected to simultaneous bilateral removal of all frontal cerebral cortex, as far back as and including the postsigmoid gyrus. Care was taken to avoid infringing on the caudate nuclei or the ventricular system. The olfactory tracts and the piriform cortex were also left intact. Such an operation can be done with insignificant loss of blood, but since an intracranial factor other than interference with the function of the frontal lobes might be considered responsible for the results obtained, control animals were subjected to bilateral removal of an equivalent amount of occipital tissue. Four series of 5 animals each were studied, 1 animal in each series being a control. No appreciable reticulocytosis occurred in the animals with occipital lesions but in all the animals with frontal lesions the reticulocyte count increased. The maximum increase was 7.1 per cent (from 0.3 to 7.4 per cent) (chart 1) and the minimum 3.75 per cent (from 4.25 to 8.0 per cent) (chart 1.). In practically all cases the response to removal of frontal cortex consisted of an almost immediate initial shower of reticulocytes and, after a latent period of about four days, a maximum response which was succeeded by lesser showers and some slight instability.

COMMENT

Bilateral removal of frontal cortex is usually followed by at least a temporary inability on the part of the animal to feed itself. In spite of careful hand watering and feeding there is generally some loss of weight, and it might be imagined that the reticulocytosis is due to hemoconcentration. Reference to the records of weight, however, revealed no inverse relation between loss of weight and increase in reticulocytes. Moreover, if hemoconcentration were the cause of the increase there

From the Department of Neurology, College of Physicians and Surgeons, Columbia University.

1. (*a*) Mettler, F. A., and Culler, E.: J. Pharmacol. & Exper. Therap. **52**:366, 1934. (*b*) Combs, J. D.; Mettler, F. A.; Spindler, J., and Mettler, C. C.: Anat. Rec. (supp.) **61**:11, 1935. (*c*) Mettler, F. A.; Mettler, C. C., and Culler, E. A.: Effects of Total Removal of the Cerebral Cortex, Arch. Neurol. & Psychiat. **34**:1238 (Dec.) 1935. (*d*) Combs, J. D.; Mettler, C. C.; Krafka, J., Jr., and Mettler, F. A.: Anat. Rec. (supp.) **64**:9, 1936. (*e*) Mettler, F. A.; Spindler, J.; Mettler, C. C., and Combs, J. D.: Disturbances in Gastro-Intestinal Function After Localized Ablations of Cerebral Cortex, Arch. Surg. **32**:618 (April) 1936. (*f*) Mettler, F. A.: Federation Proc. **1**:61, 1942.

should have been a simultaneous increase in the number of the other formed elements of the blood. Reference to the erythrocyte count failed to disclose any such parallelism but revealed instead a rapid drop in the number of red cells. Further, it was observed that the reticulocyte showers were regularly preceded by the appearance of unusual numbers of hemokoniae. These elements were first observed by the technician assisting with the work (Mrs. Cornelius Elsasser), and their appearance suggested genuine hemopoietic stimulation.

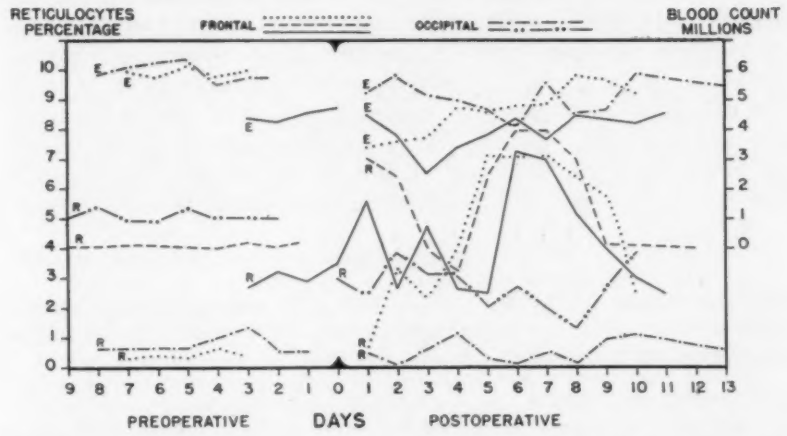


Chart 1.—Comparison of the effects of typical frontal (3 dogs) and occipital (2 dogs) operations. It will be observed that the animals with occipital lesions showed no appreciable reticulocytosis but that the reticulocyte response to frontal operation consists of a slight, immediate, unsustained rise which is followed by a more evident rise occurring after a latent period of about four days. Subsequent instability may be expected (chart 2). *E*, erythrocytes; *R*, reticulocytes.

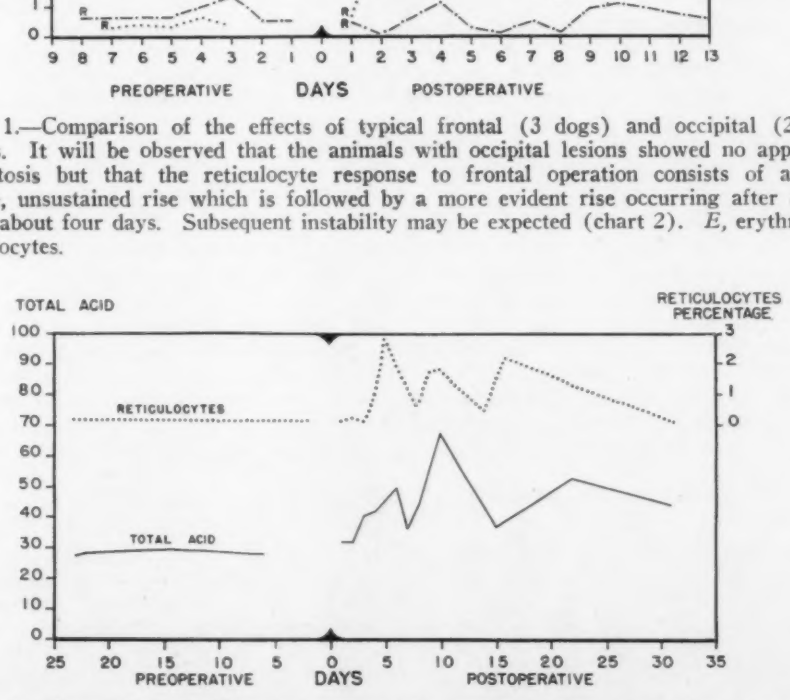


Chart 2.—Comparison of the reticulocyte and the gastric acidity curve of the same animal. While these are roughly parallel, it cannot be said that the hemopoietic response depends on the changes in acidity, since the former generally lags slightly behind the latter.

In previous experiments [1d] I have encountered a relative peripheral anemia following cortical removal. It is also known that cortical removal may be followed by blushing of the gastric mucosa, splenomegaly and increased response to epinephrine,[1e] circumstances which argue for visceral erythrocytic stagnation and may explain the peripheral anemia. In the present experiments the erythrocyte count usually dropped after frontal operation (but not after occipital operation),

sometimes declining gradually for two or three days. It is not inconceivable that visceral vasostasis may be the indirect cause of the reticulocytosis since it produces peripheral anemia, but another factor remained to be considered. By some mechanism, the nature of which is not precisely clear, removal of frontal cortex may produce gastric hyperacidity,[1d] and it is worth noting that the latent period of the maximum reticulocyte response to removal of such cortex is approximately the same as that after the administration of liver or gastric extract (three to five days). I therefore decided to follow the time relationships between the reticulocyte and the acid response after bilateral removal of frontal cortex in an animal with a previously prepared gastric fistula. The result is shown in chart 2. The characteristics of the acid curves were irregular but suggestive of those of the reticulocyte response. Simultaneous study of total acid and reticulocyte curves showed a rough parallelism, but the rise in gastric acidity generally lagged slightly behind the reticulocyte response and cannot therefore have stimulated it. Presumably both results are due to some common cause rather than dependent on each other.

CONCLUSION

Removal of frontal cerebral cortex from the dog produces a reticulocyte response not seen after other cortical operations. This is not the result of injury to subcortical nuclear areas, nor is it due to hemoconcentration.

630 West 168th Street.

REPAIR OF LARGE CRANIAL DEFECTS

REPORT OF A CASE IN WHICH A LARGE CRANIAL DEFECT WAS REPAIRED BY A GRAFT FROM THE ILIUM

VASILIOS S. LAMBROS, M.D.*
CHICAGO

From a survey of the literature [1] it appears that the fact that a large amount of bone may be obtained from the ilium as a transplant for repairing a cranial defect is not well known. The case to be reported demonstrates that a large defect of the skull may be repaired by utilizing almost the entire outer table of the ilium with only temporary impairment of function of either the pelvic bone or the muscles detached from it.

E. B. P., a 26 year old man, was referred by Dr. Thomas C. Douglas to the University of Chicago Clinics on Oct. 15, 1941. His complaint was of a bony swelling, which had been present in the right parietotemporal region for two and a half years. He stated that the mass had remained stationary in size for two years but that for the past five months it had increased in size. On May 30, 1941 he had a severe headache accompanied by a transitory slight impairment of memory. In July headaches of a sharp knifelike character developed, especially over the right parietal region. Often they were accompanied by periods of transient dizziness. The day before his admission to the hospital he experienced numbness in the fourth and fifth fingers of his left hand. This gradually spread to the rest of the hand and to the forearm. He described his arm as "being strange but not numb." At the same time he noted that the left side of his face was numb and that his tongue felt thick and difficult to maneuver. He had no muscular weakness.

Physical examination revealed a hard nonfluctuant mass, measuring 8 by 8.5 cm., over the right frontoparietal area and merging with the surrounding bone. No bruit was audible. Neurologic examination revealed no abnormality except that the left arm did not swing as much as the right.

Lateral roentgenograms of the skull demonstrated a large area of sclerosis, measuring about 9 cm. in diameter, in the right frontoparietal region. The central part of the sclerotic area was less dense than the periphery. Radiating toward the center were dense bony spicules. Tangential views of the sclerotic area showed lines of density radiating from the inner table and matrix peripherally into the mass, which had elevated and markedly thinned the outer table. The skull was approximately 4 cm. in thickness. The inner table appeared to be intact (fig. 1).

The blood and the urine were normal, and the Wassermann and Kahn reactions of the blood were both negative.

On October 24 Dr. A. E. Walker performed a right frontal craniectomy and removed a tumor, diagnosed as meningioma. A horseshoe incision was made with the base in the temporal region. The incision anteriorly followed the hair line and posteriorly was 1 to 2 cm. outside the margin of the hyperostosis. The tissues of the scalp were quite vascular, but the

---

* Fellow of the Douglas Smith Foundation.

From the Division of Neurological Surgery, University of Chicago.

1. (*a*) Mauclaire, P.: Greffes crâniennes, Arch. gén. de chir. **10**:302, 1914. (*b*) Phemister, D. B.: Personal communication to the author. (*c*) Pickerill, P.: A New Method of Osteoplastic Restoration of the Skull, M. J. Australia **2**:228, 1931. (*d*) Money, R. A.: Osteoplastic Restoration of the Skull, ibid. **2**:269, 1932. (*e*) Klages, F.: Plastische Deckung grösser Schädeldachlücken aus dem Beckenkamm, Zentralbl. f. Chir. **28**:1580, 1939. (*f*) Rehn, cited by Klages. (*g*) Klapp, cited by Klages. (*h*) Naffziger, H. C., in discussion on Grant, F. C., and Norcross, N. C.: Repair of Cranial Defects by Cranioplasty, Ann. Surg. **110**:511, 1939. (*i*) Kolodny, A.: Osteoplastic Repair of Cranial Defects, Am. J. Surg. **46**:365, 1939. (*j*) Naffziger, H. C.: The Restoration of Defects of the Skull, Ann. Surg. **104**:321, 1936. (*k*) Grant, F. C., and Norcross, N. C.: Repair of Cranial Defects by Cranioplasty, ibid. **110**:488, 1939.

bleeding was controlled without great difficulty. Perforations were placed so that two saw cuts could be made both anteriorly and posteriorly outside the involved bone. The medial limb of the bone flap was rongeured away, since it lay almost over the superior longitudinal sinus. The scalp was reflected from the hyperostosis, and the bone flap was fractured. The temporal muscle was seized with a Kocher forceps and cut so that the hyperostotic bone was removed in one piece. The cut edge of the temporal muscle was sutured to control bleeding. The exposed dura was quite firm over an area about 4 by 5 cm. in diameter, although there was relatively little bleeding from this area. The adjacent dura appeared normal in consistency. The dura was incised about 1 cm. outside the firm area, and this incision was made in normal dura mater around the entire circumference of the tumor. The tumor was carefully dissected from the brain tissue and delivered from its bed. On the

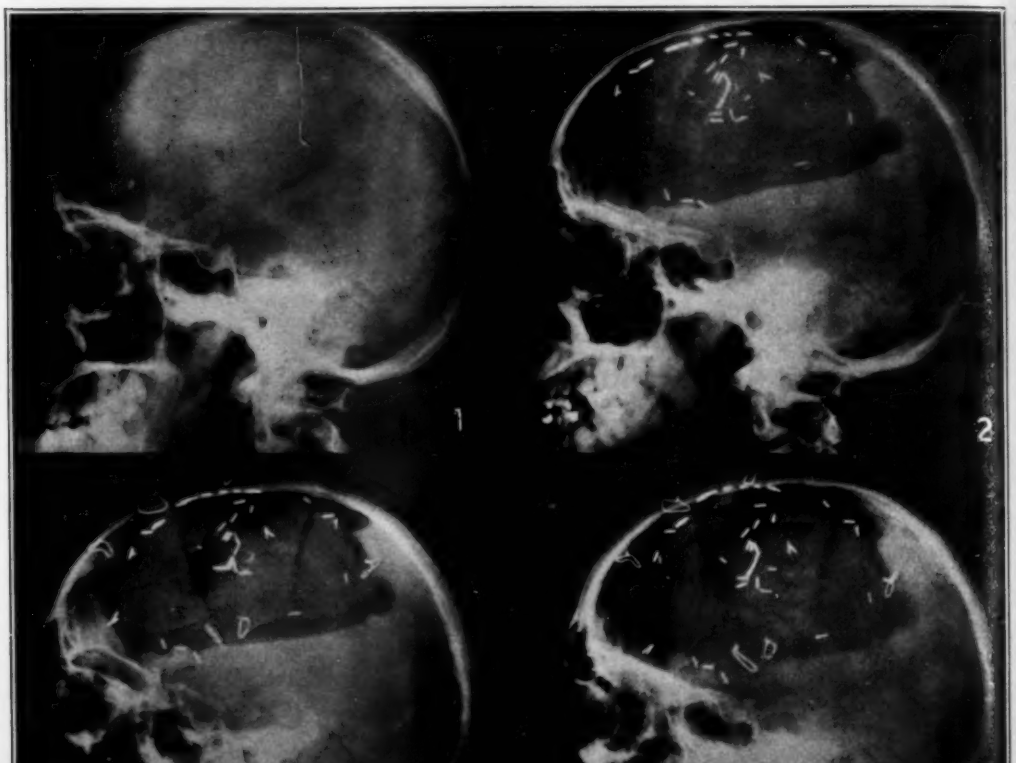


Fig. 1.—Right lateral roentgenograms of the skull taken as follows: (*1*) before operation, showing the large area of hyperostosis in the right frontal region. (*2*) after the first operation, showing the large defect following the removal of the tumor. The size of the tumor may be estimated by the outer ring of silver clips. The central group of clips are in the vascular bed of the tumor. (*3*) after the second operation, showing the defect filled with bone grafts from the external table of the ilium. (*4*) six and one-half months after the second operation, showing some absorption of the osseous grafts.

medial border it was found to be attached to the dura mater along the longitudinal sinus. It was cut away after the margin of the sinus had been clipped. A branch of the rolandic vein was clipped. On inspection the tumor seemed to be completely removed except along the anterior margin of the bony defect. Accordingly, 1 to 2 cm. of bone was rongeured from this region. A piece of fascia lata shaped to the dural defect had been removed from the right thigh; it was sutured in place with black silk. The skin was closed with two layers of sutures.

The pathologic specimens consisted of the hyperostotic bone, measuring 11.3 by 8.5 by 4.5 cm. and weighing 263 Gm., and a mass of tumor tissue attached to the dura mater, measuring 7 by 6 by 4 cm. and weighing 55 Gm.

The bone was covered on its outer convex surface with muscle and periosteum and was firm except for a soft central area 5 to 6 cm. in diameter. The concave or inner surface of the bone was roughened by fine bony trabeculations. Sectioning through the center of the bone revealed a fleshy mass 1 to 2 cm. in thickness between the bony tables.

Numerous bony spicules, usually radiating to the dome, passed through this mass. The central portion of the external table was composed almost entirely of soft tumor tissue.

Sections through the bone showed marked osseous proliferation with multiple fine bony spicules. The young bone was poorly calcified. Between the bony spicules was an intertwining mass of connective tissue, tumor cells with the same characteristics as those in the tumor proper and small amounts of normal marrow. The periosteum could be traced from the margin of the hyperostosis to its dome. The hyperostosis was infiltrated with tumor tissue, which had not penetrated the periosteum at any point.

The tumor was covered on one side by thickened trabeculated and roughened dura mater. On the opposite pole it was nodular, but the surfaces of these excrescences were smooth. Sectioning the tumor revealed coarse trabeculation with a tendency toward radiation from the dural surface. Its firm coarse-grained surface contained numerous small brown hemorrhagic areas.

The tumor was composed of lanceolate cells with medium-sized nuclei, which varied from oval to round. The cells were irregularly arranged parallel to each other or in whorls. In areas the cells were separated by clear spaces, presumably edema. There were many hyalinized areas scattered throughout, a few of which had calcospherites. In a few places the cells were enlarged and had eccentric nuclei and honeycomb cytoplasm, probably representing fatty degeneration. Reticulin was seen only surrounding the blood vessels.

The pathologic diagnosis was psammomatous meningioma with hyperostosis.

On November 8 bone was transplanted from the ilium to the defect in the skull. Dr. Walker reflected the scalp. This exposed a large cystic cavity with a smooth wall, bounded internally by the fascial transplant and externally by the subcutaneous tissue. The cavity contained xanthochromic fluid, which escaped as the cutaneous flap was reflected. The bony margin of the cavity was freshened, and the periosteum in the anteroinferior portion of the incision was cut away. Since at the previous operation the periosteum in this region was slightly thickened, and since microscopic examination of a specimen from this area had revealed evidence of tumor, the periosteum was removed to normal tissue. A rubber patch was shaped to fit the defect in the skull.

Dr. D. B. Phemister made a large horseshoe-shaped incision along the crest of the right ilium. This extended downward 4.5 cm. from the anterior and posterior iliac spines. The muscles were stripped from the entire side of the ilium. There was much oozing, but the bleeding points were controlled by catgut ligatures. The patch of rubber tissue cut to the size of the defect in the skull was laid on the side of the ilium with its long axis placed anteroposteriorly. With a narrow chisel, the graft to be cut was outlined. It was divided into three portions by making two cuts running longitudinally with the body, about one third of the distance from either end (fig. 2). With a thin, wide-beveled chisel, the tabula externa of the anterior graft, extending forward to the anterior spine, was chiseled off from above downward. This graft was slightly curved as it was cut away. The middle graft was cut from above downward in the same way, its base lying anteriorly just above the acetabulum. The entire thickness of the ilium was removed at the normally thin region; elsewhere the line of division passed through spongy bone. The posterior graft was cut from above downward, its posterior limits extending to within 2 cm. of the posterior inferior spine. There was oozing from the denuded bone, which comprised at least four fifths of the lateral surface of the ilium. The flap was reflected, and the deep fascia of the gluteal muscles was sutured along the iliac crest with interrupted chromic catgut sutures to the muscular attachments above. One Penrose drain was inserted posteriorly. The subcutaneous tissue was sutured with plain catgut and the skin with interrupted silk.

The first bone graft was fitted into place in the anterior third of the cranial defect. Perforations were made in the graft and in the margins of the defect in the skull, and the graft was held in place with silver wire. Each of the subsequent grafts was similarly fitted into the defect, the inner surface of the graft being exposed and the smooth external surface being opposed to the fascia lata (fig. 3). The skin was turned down over the roughened surface of the grafts and closed with interrupted black silk sutures, one layer being placed in the subcutaneous tissue and one layer in the skin.

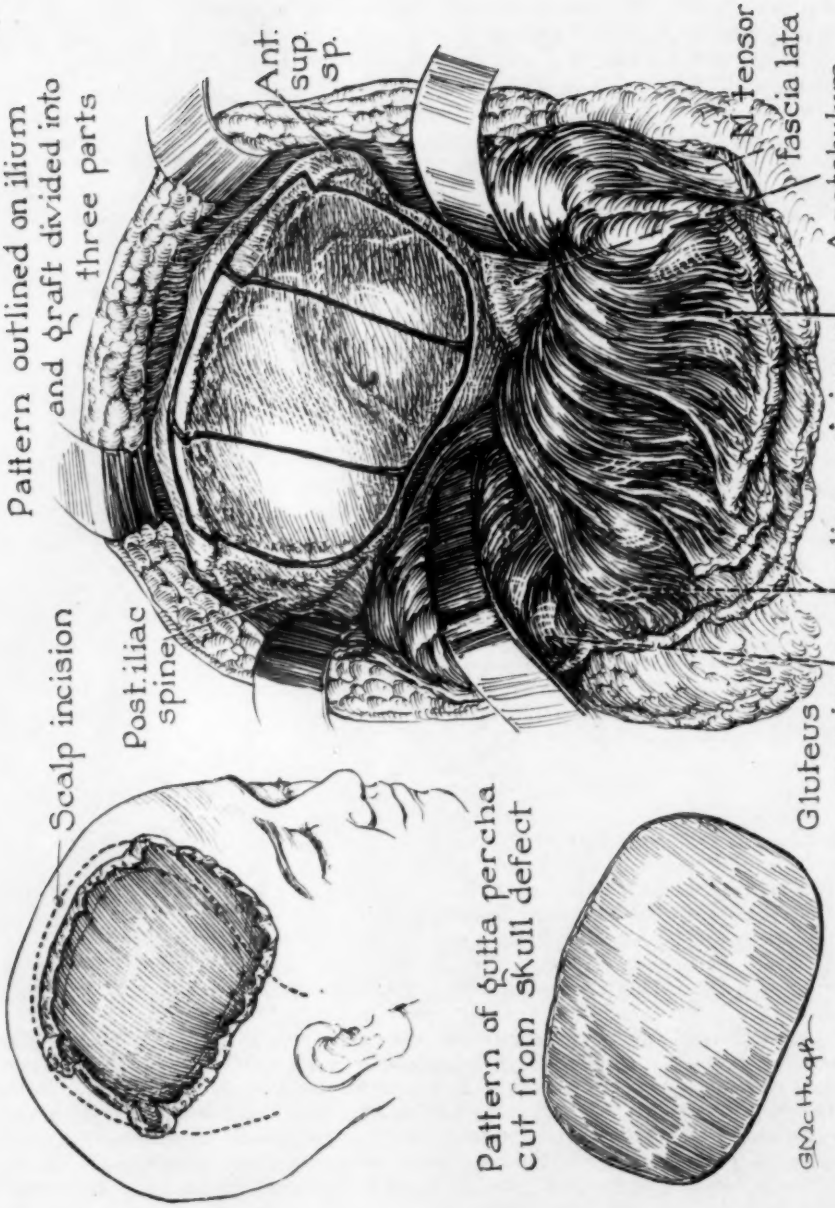


Fig. 2.—Sketches to show the operative procedures used in cranioplasty using grafts from the ilium. In the upper left hand corner the bony defect is shown, with the dural defect closed by fascia lata.

The right leg was placed in an aluminum posterior splint with a cross bar rest to prevent external rotation while the muscles were becoming reattached. The postoperative course was uneventful.

In four weeks the patient was able to walk with the aid of crutches. Two months after the second operation he had some weakness of the abductor and internal rotator muscles of the thigh. Five months after the operation he was allowed to walk without crutches.

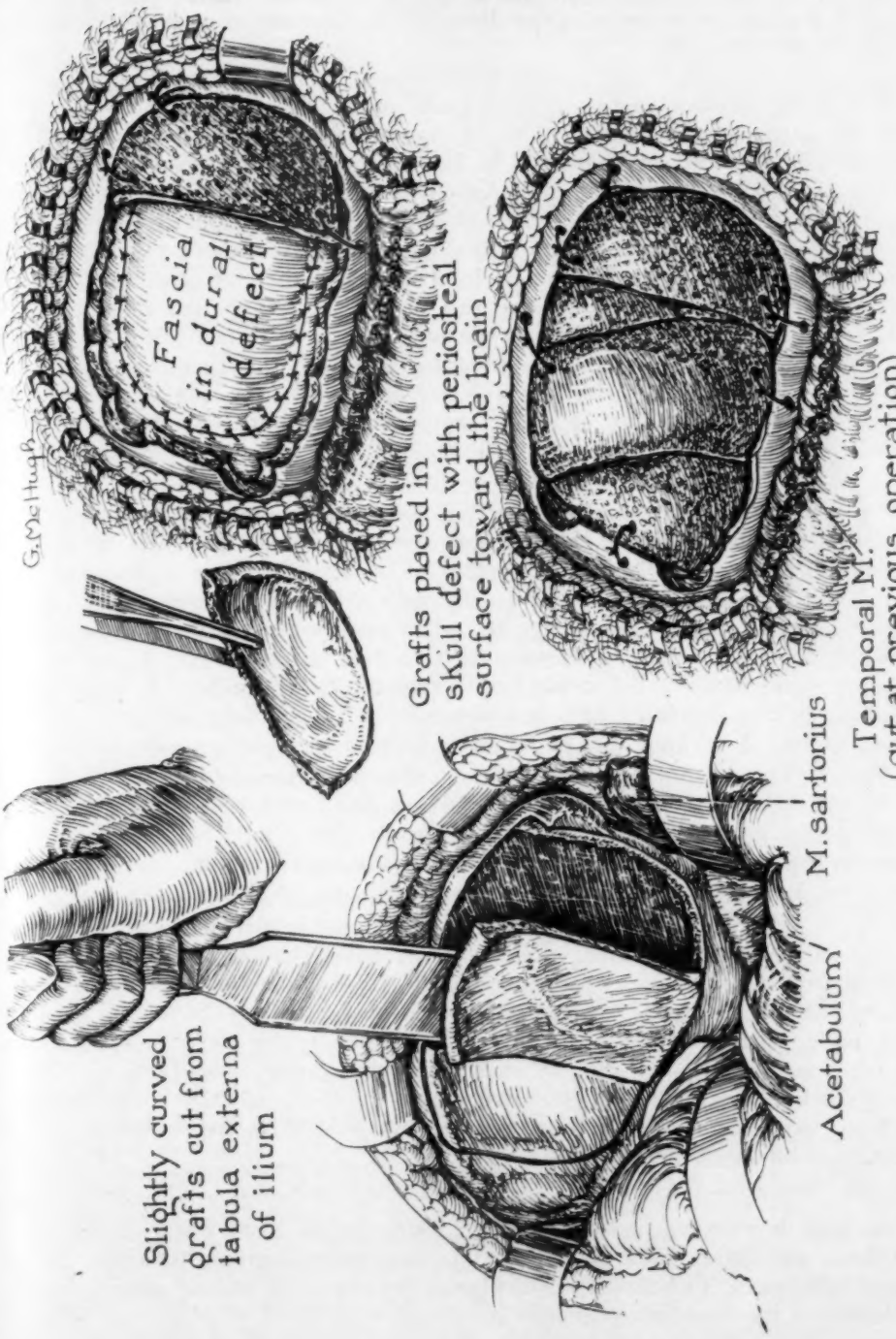

Fascia in dural defect
Grafts placed in skull defect with periosteal surface toward the brain
Temporal M. (cut at previous operation)
M. sartorius
Acetabulum
Slightly curved grafts cut from tabula externa of ilium

Fig. 3.—The placing of the bone grafts in the cranial defect.

There was still, however, slight weakness of the internal rotator muscles of the thigh. The cranial defect was well filled. Roentgenograms of the right hip showed the defect to be slowly filling.

The patient had no abnormal neurologic symptoms following the operation. When seen fifteen months after the operation he presented no abnormal neurologic signs. There was

no apparent muscular weakness, but he stated that if he carried a heavy load slight limp developed. Walking caused him no inconvenience, but he was unable to run well. The grafted area in the skull was firm.

COMMENT

It is to be emphasized that a large graft may be obtained from the ilium to cover an extensive cranial defect. The average surface available for a graft from the external table is approximately 14 to 15 by 9 to 12 cm.; that available from the table is 11 to 13.5 by 8 to 10 cm. An obvious objection is that a spontaneous fracture may develop in the ilium after the graft has been removed. In the case of a large graft there may be a limp lasting for several months as a result of weakness of the gluteal muscle. Another disadvantage is the fact that two surgical teams are necessary to carry out the two major procedures that must be performed. That the cosmetic result is superior to that obtained with the use of bone from ribs, the tibia or other more accessible parts is indisputable. However, it is no better than that which may be obtained with the use of nonosseous substances. The desirability of such a herculean procedure will depend on the ultimate fate of the graft and the relative likelihood of infection if an osseous or a nonosseous graft is used.

It is generally agreed (Naffziger [1h, j]; Kolodny [11]) that osseous transplants are eventually absorbed and that only a dense fibrous sheet is left. This layer may be sufficient to maintain the normal contour of the skull and give a good cosmetic result. Yet little protection is afforded by such a fibrous sheet of tissue. Nonosseous grafts have the disadvantage that they usually cause a certain amount of tissue reaction which may predispose to infection. If, however, a nonosseous substance could be used that would not irritate the tissues unduly, it would have the advantages of durability and ease of application, which are not possessed by osseous grafts. Vitallium [2] and tantalium have been suggested as such substances.

Walker, Taggart and Lambros [3] in this clinic have been using a plastic which can be readily molded to the desired shape and size (methyl methacrylate [4]). It evokes minimal reaction from the tissues, so that little fluid collects under the cutaneous flap. This plastic may be used at the primary operation or inserted later.

The plastic insert is prepared in the desired thickness and size and perforated every 2 cm. with a 5 mm. drill. With the aid of heat it is molded over a plaster moulage of the patient's head. While tightly bandaged on the moulage, it is sterilized in the autoclave. The plate, slightly larger than the defect, is held in place by silk sutures placed through the margin of the bone. The dura is sutured to the under surface of the scalp through the holes in the plastic. This allows approximation of the dura and the scalp, thus obliterating a dead space. Occasionally the dura mater cannot be so elevated, but the result may still be satisfactory. The scalp wound is closed without drainage. Aspiration of the wound is rarely necessary when this plastic is used.

SUMMARY

One case is reported, in which a large defect of the skull was repaired by a graft from the ilium. The technic of this procedure is given in detail. Nonosseous substances, such as an inert plastic, for repairing cranial defects would be desirable if the tissue reaction were minimal.

---

2. Peyton, W. T., and Hall, H. B.: The Repair of a Cranial Defect with a Vitallium Plate, Surgery **10**:711, 1941.

3. Walker, A. E.; Taggart, J. K., Jr., and Lambros, V. S.: Unpublished data.

4. Methyl methacrylate is manufactured by Fricke and Getz Dental Manufacturing Company, Chicago, under the trade name of Vitacrilic and by E. I. Du Pont de Nemours & Company, New York, under the trade name of Lucite.

AN EVALUATION OF THE BLOOD TEST FOR GALACTOSE TOLERANCE IN THE DIAGNOSIS OF HYPERTHYROIDISM

NORMAN G. SCHNEEBERG, M.D.

WILLIAM B. LIKOFF, M.D.
AND
DAVID R. MERANZE, M.D.
Pathologist and Director of Laboratories
PHILADELPHIA

Several reports have appeared in the literature concerning the experience of various workers with the blood test for galactose tolerance first described by Althausen and Wever in 1937.[1] We [2] have found the test to be a valuable adjunct in the diagnosis of hyperthyroidism, and it seems pertinent at this time to summarize and evaluate the results reported to date and to present our additional experience with the test.

Hirose,[3] utilizing the test for galactosuria introduced by Bauer [4] in 1906, was the first to demonstrate an impairment of galactose tolerance in thyrotoxicosis. Rowe,[5] using a modification of Bauer's test, found impaired tolerance to galactose in hyperthyroidism, hyperpituitarism, adrenal disease, ovarian and pancreatic failure and hepatic disease. Increased tolerance was noted in hypothyroidism and hypopituitarism. Rowe stressed the complex factors affecting galactose metabolism in the human economy and believed that the tolerance as measured with his technic represented the algebraic sum of several reenforcing and antagonistic agencies.

The description of a method for the quantitative determination of galactose in blood by Raymond and Blanco [6] in 1928 provided the impetus for the clinical investigation of galactose tolerance by means of blood tests. Harding and Grant [7] administered 40 Gm. of galactose to 16 normal male subjects and concluded that the peak of the concentration of galactose in the blood was usually not more than

---

From the Laboratories and Wards of the Mount Sinai Hospital.

1. Althausen, T. L., and Wever, G. K.: Galactose Tolerance in Hyperthyroidism, J. Clin. Investigation **16**:257-259 (March) 1937.

2. Meranze, D. R.; Likoff, W. B., and Schneeberg, N. G.: The Blood Galactose Tolerance Test, Am. J. Clin. Path. **12**:261-271 (May) 1942.

3. Hirose, M.: Ueber die alimentäre Galaktosurie bei Leberkrankheiten und Neurosen, Deutsche med. Wchnschr. **38**:1414, 1912; cited by MacLagan.[18]

4. Bauer, R.: Weitere Untersuchungen über alimentäre Galaktosurie, Wien. med. Wchnschr. **56**:2537-2545, 1906; cited by Rowe and McManus.[5e]

5. (*a*) Rowe, A. W.: Metabolism of Galactose: Threshold of Tolerance in Normal Adults, Arch. Int. Med. **34**:388-401 (Sept.) 1924; (*b*) Metabolism of Galactose: Influence of Disturbed Endocrine Function, Am. J. M. Sc. **190**:686-700 (Nov.) 1935; (*c*) Metabolism of Galactose: Influence on Tolerance of Coexisting Endocrinopathies, ibid. **190**:701-708 (Nov.) 1935. (*d*) Rowe, A. W., and McGuiness, M.: Metabolism of Galactose: Effect on Tolerance of Level of Ovarian Activity, Am. J. Obst. & Gynec. **16**:687-698 (Nov.) 1928. (*e*) Rowe, A. W., and McManus, M.: Metabolism of Galactose: Influence of Hepatic Dysfunction on Tolerance, Am. J. M. Sc. **181**:777-788 (June) 1931.

6. Raymond, A. L., and Blanco, J. G.: Blood Sugar Determination and Separation of Sugars with Live Yeast, J. Biol. Chem. **80**:631-642 (Dec.) 1928.

7. Harding, V. J., and Grant, G. A.: The Metabolism of Galactose, J. Biol. Chem. **99**: 629-646 (Jan.) 1933.

30 mg. per hundred cubic centimeters but occasionally increased to 60 mg. Althausen and his associates [8] first applied the blood test for galactose tolerance to the study of hyperthyroidism, and the technic they described has been followed, with slight modifications, by subsequent workers. They considered a concentration of 10 to 30 mg. per hundred cubic centimeters of blood normal after the oral administration of 40 Gm. of galactose. Values below 10 mg. represented increased tolerance and over 30 mg. depressed tolerance; the 30 to 40 mg. range was found to represent values of doubtful interpretation. One hundred and twenty-four hyperthyroid patients so tested revealed depressed tolerance; in 5 patients the tests gave doubtful results, and in 1 the result was normal. Hepatic insufficiency and Paget's disease were presented as the only two clinical conditions that might interfere with the test in the diagnosis of thyrotoxicosis, since both of these conditions produced consistent depressions in tolerance. On the basis of experimental work on animals [9] and the demonstration of normal tolerance to intravenously administered galactose in 10 patients with hyperthyroidism in whom oral administration had revealed the usual impaired tolerance,[8a] Althausen concluded that the absorption of galactose from the intestine was accelerated in thyrotoxic subjects. He suggested that the thyroid hormone influenced absorption of galactose mainly by accelerating its rate of phosphorylation. His advocacy of the blood test for galactose tolerance as an adequate clinical test of intestinal absorption [10] was followed shortly by the demonstration by Beams, Free and Glenn [11] of decreased intestinal absorption of galactose in patients with deficiency diseases, such as pellagra, nontropical sprue and rosacea keratitis. In England, MacLagan viewed the test as a means of estimating hepatic function [12] and found it useful in the differential diagnosis of jaundice [13] and in judging hepatic dysfunction in thyrotoxicosis.[14] Thirty of his 41 subjects with thyrotoxicosis revealed definite impairment in galactose tolerance, and the remaining 11 all had results above the normal average. MacLagan's criteria for normal and abnormal values differed widely from those noted by Althausen and by us, since his upper limit of normal was 80 mg. per hundred cubic centimeters. Variations in technic appear insufficient to account for the wide difference in the normal values obtained by the two groups. Wilson,[15] adhering to the technic and standards reported by MacLagan, found values above 40 mg. for 22 of 24 thyrotoxic patients; 1 patient had values in the 30 to 40 mg. range and 1 a peak of only 9 mg. Despite Wilson's adherence to MacLagan's standards, his values for subjects with hyperthyroidism closely paralleled those of Althausen and of other American workers. We [2] studied 162 subjects, 36 of whom were hyperthyroid. Only 1 of these revealed normal

8. (*a*) Althausen, T. L.; Lockhart, J. C., and Soley, M. H.: New Diagnostic Test (Galactose) for Thyroid Disease, Am. J. M. Sc. **199**:342-351 (March) 1940. (*b*) Althausen and Wever.[1]

9. Althausen, T. L., and Stockholm, M.: Influence of the Thyroid Gland on Absorption in the Digestive Tract, Am. J. Physiol. **123**:577-588 (Sept.) 1938.

10. Althausen, T. L.: A Test for Intestinal Absorption, Am. J. Digest. Dis. **6**:544-549 (Oct.) 1939.

11. Beams, A. J.; Free, A. H., and Glenn, P. M.: The Absorption of Galactose from the Gastro-Intestinal Tract in Deficiency Diseases, Am. J. Digest. Dis. **8**:415-421 (Nov.) 1941.

12. MacLagan, N. F.: Galactose Tolerance as a Test of Liver Function, Quart. J. Med. **9**:151-162 (April) 1940.

13. MacLagan, N. F.: Galactose Tolerance in Jaundice and Hyperthyroidism, Proc. Roy. Soc. Med. **34**:602-606 (July) 1941.

14. MacLagan, N. F.; Rundle, F. F.; Collard, H. B., and Mills, F. H.: Liver Function in Thyrotoxicosis, Quart. J. Med. **9**:215-228 (July) 1940.

15. Wilson, T. E.: The Galactose Tolerance Test in Thyrotoxicosis, M. J. Australia **1**: 33-44 (Jan. 10) 1942.

galactose tolerance. However, because of the discovery of depressed galactose tolerance in a heterogeneous collection of disease entities, we stressed the value of normal results in excluding the diagnosis of hyperthyroidism rather than the value of abnormal results in establishing that diagnosis. Smith, Jondahl and Ochsner [16] found 1 normal test (doubtful zone) among 41 hyperthyroid patients studied. Of 20 persons with hyperthyroidism studied by Rosenkrantz, Bruger and Lockhart [17] normal tolerance was found in 1; they too pointed out various nonthyroid states associated with depressed galactose tolerance.

The detailed technic of the test has been described elsewhere.[18] Briefly, the concentration of galactose in samples of venous or capillary blood is determined thirty and sixty minutes after the oral administration of 40 Gm. of galactose to a patient who has fasted overnight. Galactose values are obtained by yeast fermentation of the dextrose in the blood and determination of the residual reducing substances. A fixed dose (40 Gm.) of galactose has been advocated [8] because it exceeds the capacity for intestinal absorption during the period of the test. The results obtained with doses of sugars varying with body weight or surface have proved disappointing from the standpoint of uniformity,[7] though some authors [19] have maintained that this method is more accurate. Repetition of the test on the same person revealed excellent uniformity of successive determinations.[18]

Galactose is absorbed by phosphorylation in the intestine without transformation and its absorption, within wide limits, is independent of its intestinal concentration and of gastric emptying time.[10] It is absent in the blood of normal fasting subjects,[7] is not utilized as galactose by the tissues but must be converted first to dextrose in the liver,[15] is uninfluenced by insulin,[19a] is a well utilized sugar when given in small amounts [20] and is not retained by any renal threshold.[21] The factor of age per se, investigated by Rosenkrantz, Bruger and Lockhart,[17] appeared to exert little influence on galactose tolerance.

Though Althausen established a definite range of values for tolerance tests in normal subjects,[8] an analysis of the results (table 1) obtained by other workers reveals a wider range of normal values in individual instances. Twenty-two (23.4 per cent) of the 94 normal persons individually tabulated had galactose values above 30 mg. per hundred cubic centimeters, and 6 (6.4 per cent) had values under 10 mg.

Since our first publication [2] we have performed additional tests, bringing the total number to 220 subjects, of whom 48 had definite clinical hyperthyroidism. Forty-five of these 48 subjects had values above 40 mg. per hundred cubic centimeters; 2 had values in the doubtful 30 to 40 mg. zone, and 1 had a normal concentration. The average of the peaks was 84.2 mg., with a range of 25.4 to 150 mg. The one normal result was obtained for a 40 year old woman whose basal metabolism was over + 30 per cent on two occasions and whose peak blood galactose value was 25.4 mg. She improved considerably after subtotal thyroid-

16. Smith, M. C.; Jondahl, W., and Ochsner, A.: The Significance of the Galactose Tolerance Test in Hyperthyroidism, Surg., Gynec. & Obst. **74**:1083-1086 (June) 1942.

17. Rosenkrantz, J. A.; Bruger, M., and Lockhart, A. J.: Studies on Galactose Tolerance with Especial Reference to Thyroid Disease, Am. J. M. Sc. **204**:36-41 (July) 1942.

18. Meranze, Likoff and Schneeberg.[2] Althausen, Lockhart and Soley.[8]

19. (*a*) Roe, J. H., and Schwartzman, A. S.: Galactose Tolerance of Normal and Diabetic Subjects, and Effect of Insulin upon Galactose Metabolism, J. Biol. Chem. **96**:717-735 (June) 1932. (*b*) Beams, Free and Glenn.[11]

20. Harding, V. J., and van Nostrand, F. H.: Variations in Blood and Urinary Sugar After Ingestion of Galactose, J. Biol. Chem. **85**:765-778 (Feb.) 1930.

21. Folin, O., and Berglund, H.: Transportation, Retention and Excretion of Carbohydrates, J. Biol. Chem. **51**:213-273 (March) 1922.

ectomy, and microscopic examination of the gland revealed moderate hyperplasia. Fifteen months later the test was repeated and revealed a galactose peak of 50.8 mg., though the patient was symptom free. Table 2 summarizes the results reported in the literature for 304 thyrotoxic patients and reveals positive results in 280 cases (92.1 per cent).

We have failed to confirm the reported prompt return to normal of the galactose tolerance of patients after thyroidectomy. Althausen [8] repeated the test "at the time of discharge from the hospital" for 22 patients and found that 18 (82 per cent) had returned to normal. Twelve of 16 patients so investigated by MacLagan [14]

TABLE 1.—*Values Reported by Various Authors for Galactose in the Blood of Normal Subjects*

	Number of Subjects					Range of Values, Mg. per 100 Cc.
	Total	Below 10 Mg.	10-30 Mg.	30-40 Mg.	Over 40 Mg.	
Althausen, Lockhart and Soley [6]; Althausen [10]	21	..	20	1 (above 30)		13-31
Harding and Grant [7]	16	4	7	2	3	8-70
MacLagan [13]	50 normal persons—individual results not stated					Up to 80
Wilson [15]	..	..	..	..	..	....
Meranze, Likoff and Schneeberg [2]	10	2	8	..	..	5-27
Smith, Jondahl and Ochsner [16]	10 normal persons—individual results not stated					9-41
Rosenkrantz, Bruger and Lockhart [17]	47*	..	31	16 (above 30)		2-92
Totals	94	6	66	22		

* Twenty-four persons over 50 years of age and 23 persons under 50 years without evidence of hyperthyroidism, liver disease or nephritis.

TABLE 2.—*Reported Results in Thyrotoxic Patients*

	Number of Subjects					Range of Values, Mg. per 100 Cc.
	Total	Below Normal	Normal	Doubtful	High	
Althausen, Lockhart and Soley [8]	130	..	1	5	124	25-152
*MacLagan [13]; MacLagan, Rundle, Collard and Mills [14]	41	..	11	(?)	30	.....
*Wilson [15]	24	1	..	1	22	9-136
Meranze, Likoff and Schneeberg [2]	48	..	1	2	45	25.4-150
Rosenkrantz, Bruger and Lockhart [17]	20	..	1	..	19	17-136
Smith, Jondahl and Ochsner [16]	41	..	..	1	40	.....
Totals	304	1	14	9	280	

* Normal values of these authors are above the 10 to 30 mg. normal range of American workers.

showed a "striking decrease in . . . galactose values . . . two weeks postoperatively." Wilson [15] included 6 patients in his tabulated results on whom the test was performed "after subtotal thyroidectomy" but does not record the interval. The galactose peaks for 3 of these 6 patients were over 40 mg., and a fourth peak was 32 mg. We repeated the test on 18 patients with hyperthyroidism ten to fourteen days after subtotal thyroidectomy and found normal values in only 3 patients. In 12 of the 15 patients in whom depressed tolerance to galactose persisted the basal metabolic rate had returned to normal, and in the remaining 3 the metabolism had been appreciably reduced by the operation. In addition, the test was performed on 15 patients on whom thyroidectomy had been done one to eight years previously. We had not the opportunity to perform preoperative tests. Ten of the 15 subjects showed depressed galactose tolerance. Despite these findings, for only 1 of these 15 persons was a second thyroidectomy considered

necessary. This permanency of altered galactose tolerance in such a large percentage of patients makes the test, in our experience, unreliable as a diagnostic aid when a recurrence of thyrotoxicosis is suspected.

The test is found especially helpful in excluding the diagnosis of hyperthyroidism in those patients in whom hypermetabolism (basal metabolic rate over + 20 per cent) and certain suggestive signs and symptoms of thyrotoxicosis coexist. In several such instances the implications of the normal galactose tolerance have been corroborated by further study and observation. Patient 1 was a woman three months pregnant with a basal metabolic rate of + 29 per cent, a peak galactose of 11.1 mg. and clinical signs suggestive of hyperthyroidism. She failed to improve after subtotal thyroidectomy, and pathologic examination of the thyroid revealed a normal gland. Patient 2 had a small goiter, hypermetabolism and normal galactose tolerance. Operation was performed without benefit to the patient, and microscopic examination of the gland failed to reveal any evidence of thyroid hyperactivity. Patient 3, a 41 year old man with mild hypertension, was similarly thyroidectomized for suggestive toxic symptoms and signs and because of an elevated basal metabolic rate (plus 29 per cent). His blood galactose peak was 24.8 mg. When seen four months later he was clinically unimproved. One of us (D. R. M.) reported a "moderately colloid goiter." In 2 similar cases, surgical intervention was contemplated but was postponed when a period of rest in bed reduced the hypermetabolism and tachycardia to normal limits. Patients with severe hypertension frequently have elevated basal metabolic rates, readings of + 25 per cent or higher not being uncommon.[22] In 5 such patients with normal galactose tolerance, hypermetabolism, provisionally ascribed to thyrotoxicosis, was found to be incidental to compensated hypertensive cardiovascular disease. In cases of various functional and psychogenic disorders hyperthyroidism is frequently suspected, and if hypermetabolism coexists the differential diagnosis becomes difficult. In 2 such instances, the implication of the normal results obtained in galactose tolerance tests was soon strengthened by the clinical course of the patients. Of 21 patients with various psychogenic disorders (anxiety neuroses, hysterias, etc.) 18 revealed normal galactose tolerance; the galactose peaks of the remaining 3 were 37.2, 48.9 and 91.7 mg.

Both MacLagan [14] and Wilson [15] found galactose tolerance relatively unaffected by iodine therapy and indicated the value of the test in diagnosing thyrotoxicosis in patients who were first seen with normal basal metabolic rates after a course of iodine therapy. Smith, Jondahl and Ochsner [16] noted, however, that when patients with hyperthyroidism showed a good clinical response to preoperative management and medication the galactose curve tended to approach normal, though not in direct proportion to the basal metabolic rate. We tested 5 hyperthyroid patients on the day before operation after iodine therapy. In 4 of these 5 patients high galactose values persisted. These results tend to substantiate the findings of MacLagan and Wilson.

Galactose peaks below 10 mg. were reported by Althausen [8] and by Smith [16] in myxedema and by Beams [11] in various deficiency diseases.

To insure the logical use of any laboratory test, the physician must be well informed concerning factors which may complicate the interpretation of the results of that test. Althausen [8a] believed that only advanced hepatic insufficiency and Paget's disease would interfere with the use of the galactose test for the diagnosis of hyperthyroidism. We [2] described abnormal galactose tolerance in a greater

22. Yater, W. M.: The Fundamentals of Internal Medicine, New York, D. Appleton-Century Co., Inc., 1938, p. 477.

ectomy, and microscopic examination of the gland revealed moderate hyperplasia. Fifteen months later the test was repeated and revealed a galactose peak of 50.8 mg., though the patient was symptom free. Table 2 summarizes the results reported in the literature for 304 thyrotoxic patients and reveals positive results in 280 cases (92.1 per cent).

We have failed to confirm the reported prompt return to normal of the galactose tolerance of patients after thyroidectomy. Althausen [8] repeated the test "at the time of discharge from the hospital" for 22 patients and found that 18 (82 per cent) had returned to normal. Twelve of 16 patients so investigated by MacLagan [14]

TABLE 1.—*Values Reported by Various Authors for Galactose in the Blood of Normal Subjects*

	Number of Subjects					Range of Values, Mg. per 100 Cc.
	Total	Below 10 Mg.	10-30 Mg.	30-40 Mg.	Over 40 Mg.	
Althausen, Lockhart and Soley [8]; Althausen [10]	21	..	20	1 (above 30)		13-31
Harding and Grant [7]	16	4	7	2	3	8-70
MacLagan [13]	50 normal persons—individual results not stated					Up to 80
Wilson [15]	..	..	..	..	..	....
Meranze, Likoff and Schneeberg [2]	10	2	8	..	..	5-27
Smith, Jondahl and Ochsner [16]	10 normal persons—individual results not stated					9-41
Rosenkrantz, Bruger and Lockhart [17]	47*	..	31	16 (above 30)		2-92
Totals	94	6	66	22		

* Twenty-four persons over 50 years of age and 23 persons under 50 years without evidence of hyperthyroidism, liver disease or nephritis.

TABLE 2.—*Reported Results in Thyrotoxic Patients*

	Number of Subjects					Range of Values, Mg. per 100 Cc.
	Total	Below Normal	Normal	Doubtful	High	
Althausen, Lockhart and Soley [8]	130	..	1	5	124	25-152
*MacLagan [13]; MacLagan, Rundle, Collard and Mills [14]	41	..	11	(?)	30	.....
*Wilson [15]	24	1	..	1	22	9-136
Meranze, Likoff and Schneeberg [2]	48	..	1	2	45	25.4-150
Rosenkrantz, Bruger and Lockhart [17]	20	..	1	..	19	17-136
Smith, Jondahl and Ochsner [16]	41	..	..	1	40	.....
Totals	304	1	14	9	280	

* Normal values of these authors are above the 10 to 30 mg. normal range of American workers.

showed a "striking decrease in . . . galactose values . . . two weeks postoperatively." Wilson [15] included 6 patients in his tabulated results on whom the test was performed "after subtotal thyroidectomy" but does not record the interval. The galactose peaks for 3 of these 6 patients were over 40 mg., and a fourth peak was 32 mg. We repeated the test on 18 patients with hyperthyroidism ten to fourteen days after subtotal thyroidectomy and found normal values in only 3 patients. In 12 of the 15 patients in whom depressed tolerance to galactose persisted the basal metabolic rate had returned to normal, and in the remaining 3 the metabolism had been appreciably reduced by the operation. In addition, the test was performed on 15 patients on whom thyroidectomy had been done one to eight years previously. We had not the opportunity to perform preoperative tests. Ten of the 15 subjects showed depressed galactose tolerance. Despite these findings, for only 1 of these 15 persons was a second thyroidectomy considered

necessary. This permanency of altered galactose tolerance in such a large percentage of patients makes the test, in our experience, unreliable as a diagnostic aid when a recurrence of thyrotoxicosis is suspected.

The test is found especially helpful in excluding the diagnosis of hyperthyroidism in those patients in whom hypermetabolism (basal metabolic rate over + 20 per cent) and certain suggestive signs and symptoms of thyrotoxicosis coexist. In several such instances the implications of the normal galactose tolerance have been corroborated by further study and observation. Patient 1 was a woman three months pregnant with a basal metabolic rate of + 29 per cent, a peak galactose of 11.1 mg. and clinical signs suggestive of hyperthyroidism. She failed to improve after subtotal thyroidectomy, and pathologic examination of the thyroid revealed a normal gland. Patient 2 had a small goiter, hypermetabolism and normal galactose tolerance. Operation was performed without benefit to the patient, and microscopic examination of the gland failed to reveal any evidence of thyroid hyperactivity. Patient 3, a 41 year old man with mild hypertension, was similarly thyroidectomized for suggestive toxic symptoms and signs and because of an elevated basal metabolic rate (plus 29 per cent). His blood galactose peak was 24.8 mg. When seen four months later he was clinically unimproved. One of us (D. R. M.) reported a "moderately colloid goiter." In 2 similar cases, surgical intervention was contemplated but was postponed when a period of rest in bed reduced the hypermetabolism and tachycardia to normal limits. Patients with severe hypertension frequently have elevated basal metabolic rates, readings of + 25 per cent or higher not being uncommon.[22] In 5 such patients with normal galactose tolerance, hypermetabolism, provisionally ascribed to thyrotoxicosis, was found to be incidental to compensated hypertensive cardiovascular disease. In cases of various functional and psychogenic disorders hyperthyroidism is frequently suspected, and if hypermetabolism coexists the differential diagnosis becomes difficult. In 2 such instances, the implication of the normal results obtained in galactose tolerance tests was soon strengthened by the clinical course of the patients. Of 21 patients with various psychogenic disorders (anxiety neuroses, hysterias, etc.) 18 revealed normal galactose tolerance; the galactose peaks of the remaining 3 were 37.2, 48.9 and 91.7 mg.

Both MacLagan [14] and Wilson [15] found galactose tolerance relatively unaffected by iodine therapy and indicated the value of the test in diagnosing thyrotoxicosis in patients who were first seen with normal basal metabolic rates after a course of iodine therapy. Smith, Jondahl and Ochsner [16] noted, however, that when patients with hyperthyroidism showed a good clinical response to preoperative management and medication the galactose curve tended to approach normal, though not in direct proportion to the basal metabolic rate. We tested 5 hyperthyroid patients on the day before operation after iodine therapy. In 4 of these 5 patients high galactose values persisted. These results tend to substantiate the findings of MacLagan and Wilson.

Galactose peaks below 10 mg. were reported by Althausen [8] and by Smith [16] in myxedema and by Beams [11] in various deficiency diseases.

To insure the logical use of any laboratory test, the physician must be well informed concerning factors which may complicate the interpretation of the results of that test. Althausen [8a] believed that only advanced hepatic insufficiency and Paget's disease would interfere with the use of the galactose test for the diagnosis of hyperthyroidism. We [2] described abnormal galactose tolerance in a greater

22. Yater, W. M.: The Fundamentals of Internal Medicine, New York, D. Appleton-Century Co., Inc., 1938, p. 477.

variety of disease entities, and our subsequent experience has confirmed this observation. We too observed abnormal galactose tolerance in cases of advanced hepatic insufficiency. In all the 11 cases of hepatocellular jaundice investigated and in 3 cases of cirrhosis of the liver the tests gave positive results. The peak galactose level reached in our 1 case of Paget's disease was 31.6 mg. The combination of hypermetabolism, cardiac decompensation and certain signs suggestive of thyrotoxicosis frequently exists and may present a confusing diagnostic problem. The blood test for galactose tolerance, in our hands, has proved to be of no value in such instances. The following case is cited to illustrate this point:

L. L., a white man 54 years of age, was observed in March 1940 in decompensation secondary to hypertensive cardiovascular disease. He complained of nervousness and hyperhidrosis. Mild exophthalmos was present. His basal metabolic rate, on many observations, averaged + 34 per cent. The peak of blood galactose was 47 mg. per hundred cubic centimeters, and the level of cholesterol in the blood, as determined by Bloor's test, was 172 mg. per hundred cubic centimeters. His basal metabolic rate remained high, and he failed to improve after treatment with iodine. In November 1940 the basal metabolic rate was + 30 per cent and two galactose tests done seven days apart showed peaks of 45.8 and 80.1 mg. In November 1941 the galactose peak was 44 mg. The thyroid gland, obtained at autopsy in August 1942, was normal grossly and microscopically.

Blood galactose tolerance tests revealed depressed tolerance in 13 of 23 patients during mild cardiac decompensation; 4 patients had values in the doubtful zone, and 6 had normal values. In 7 of these 23 patients hypermetabolism was also present; 4 of the 7 in addition had depressed galactose tolerance. Of 8 patients hospitalized for active peptic ulcer, 5 had depressed tolerance to galactose, 1 had a value in the doubtful zone and 2 had normal values. In table 3 a great variety of heterogeneous disease entities in which various authors found depressed galactose tolerance are tabulated. Rosenkrantz, Bruger and Lockhart [17] mentioned Bright's disease, infections of the upper respiratory tract, impaired hepatic function, malignant disease and therapy with sulfonamide compounds as conditions very frequently producing impairment in galactose tolerance. We feel that when in cases of suspected hyperthyroidism the presence of hepatic insufficiency, cardiac decompensation, Paget's disease and peptic ulcer can be eliminated and a history of a previous thyroidectomy for hyperthyroidism is not obtained the impaired galactose tolerance is very likely due to thyrotoxicosis.

We have mentioned the two theories that have been offered to explain the mechanism of the test, (1) accelerated intestinal absorption [23] and (2) hepatic dysfunction.[12] Althausen short-circuited the gastrointestinal tract by intravenous administration of galactose and found normal values in the blood of 10 persons with hyperthyroidism who had had high blood values with the oral test. We retested 5 patients with hyperthyroidism by a technic described by Althausen [24] for intravenous administration of galactose, but in all 5 cases the galactose values were still appreciably elevated. As a control 5 intravenous tests were done on 5 normal subjects who on previous testing had shown normal tolerance for orally administered galactose. In all 5 subjects values were normal.

We were unable to find any correlation between the results of the bromsulphalein and/or the hippuric acid synthesis test and those of the blood galactose tolerance test in 45 patients so studied. Thus of 38 patients in this group who showed depressed tolerance to galactose, 20 had normal hepatic function and 18 had abnormal hepatic function as evaluated by these tests. Of the 7 patients with normal galactose tolerance in this group, 3 had normal hepatic function and 4 had

23. Althausen, Lockhart and Soley.[8] Althausen and Stockholm.[9] Althausen.[10]
24. Althausen, T. L.: Personal communication to the author.

abnormal function. Wilson,[15] too, was unable to demonstrate any correlation between tests of hepatic function and galactose tolerance. Lichtman [25] performed the urine galactose tolerance test on 13 patients with thyrotoxicosis and found that 6 of them (46 per cent) had abnormal excretion of galactose (3 to 12.5 Gm.), which he believed indicated hepatic dysfunction incident to thyrotoxicosis. Wilson [15] noted abnormal galactosuria in 8 of his 24 hyperthyroid patients (33

TABLE 3.—*Heterogeneous Diseases with Abnormal Galactose Tolerance*

Disease	Totals	Below 10 Mg.	Normal	Doubtful	High
Hepatocellular jaundice	54	..	..	..	54
Cirrhosis of the liver	6	..	..	..	6
Carcinoma of the liver	1	..	..	..	1
Hemochromatosis	1	..	..	..	1
Obstructive jaundice	28	..	17	1	10
Cholecystitis	3	..	1	..	2
Cardiac decompensation	31	..	13	4	14
Hypertensive cardiovascular disease	6	..	2	..	4
Rheumatic heart disease	3	..	2	..	1
Idiopathic tachycardia	1	..	..	1	..
Peptic ulcer	11	..	4	1	6
Intestinal hypermotility	5	1	3	..	1
Amebiasis	2	..	..	1	1
Tuberculous ileitis	1	..	..	..	1
Idiopathic diarrhea	1	..	..	..	1
Cushing's syndrome	5	1	3	..	1
Hyperinsulinism	4	..	2	1	1
Diabetes mellitus	37	7	25	2	3
Menopause	4	1	..	..	3
Psychogenic disorders	48	4	35	3	6
Paget's disease	19	..	4	..	15
Pott's disease	1	..	..	..	1
Dyschondroplasia	1	..	..	..	1
Milkman's syndrome	1	..	..	..	1
Osteosarcoma	2	..	1	..	1
Pernicious anemia	10	3	4	1	2
Pellagra	9	5	1	..	3
Nephritis	7	..	1	6 patients	"Average curve high"
Rosacea keratitis	4	2	..	1	1
Simple goiter, nontoxic adenoma, etc.	25	5	14	3	3
Urticaria	1	..	..	..	1
Fever, origin unknown	2	..	..	..	2
Infection of upper respiratory tract	9	..	..	"Average curve high"	
Pulmonary tuberculosis	3	..	..	1	2
Pneumonia (convalescent after therapy with sulfonamide compounds)	2	..	..	..	2
Congenital syphilis with chronic mastitis	1	..	..	..	1
Bronchiectasis	1	..	..	..	1
Iodine poisoning	1	..	..	..	1
Dystonia musculorum deformans	1	..	..	..	1
Hypertrophied tonsils	1	..	..	..	1

per cent) so tested. We simultaneously measured levels of galactose in the blood and output of galactose in the urine of 25 patients with various diseases. For 15 of them there was a correlation between the result of the blood test and that of the urine test (i. e., an elevated blood galactose level with excess galactosuria) and 10 revealed a lack of correlation. Of the 6 thyrotoxic patients in this group,

25. Lichtman, S. S.: Liver Function in Hyperthyroidism, with Special Reference to the Galactose Tolerance Test, Ann. Int. Med. **14**:1199-1215 (Jan.) 1941.

only 1 was found to have abnormal excretion of galactose (5.43 Gm. in five hours). The aforementioned experimental results cannot therefore be interpreted as supporting unequivocally either theory of the mechanism of the test.

SUMMARY AND CONCLUSIONS

Three hundred and four cases of thyrotoxicosis in which the blood galactose tolerance test was performed have been collected from the literature. Two hundred and eighty (92.1 per cent) of the tests yielded positive results.

The test is useful in excluding the presence of hyperthyroidism in patients with hypermetabolism due to causes other than hyperthyroidism.

The test is unreliable in the diagnosis of hyperthyroidism in patients in whom thyroidectomy has previously been required for hyperthyroidism, in patients with decompensated cardiac disease and in patients suffering with peptic ulcer, hepatic insufficiency or Paget's disease.

The fact that the result of the test may be positive in any one of the heterogeneous disease entities presented and is rarely negative in the presence of hyperthyroidism emphasizes the value of the test in excluding the diagnosis of hyperthyroidism rather than in establishing that diagnosis.

In instances in which an estimation of the basal metabolic rate cannot be performed, the blood galactose test may be substituted.

The mechanism of the altered galactose tolerance in hyperthyroidism does not appear to have been definitely established. Therefore we believe that Rowe's contention that galactose tolerance depends on a multiplicity of complex factors influencing galactose metabolism is the most fruitful concept thus far advanced in the interpretation of the test.

Miss Dorothy Bunting, record room librarian of the Mt. Sinai Hospital, cooperated in the preparation of this paper, and Miss Violet Parnes gave technical assistance.

Fifth and Reed Streets.

SPECIAL NUMBER

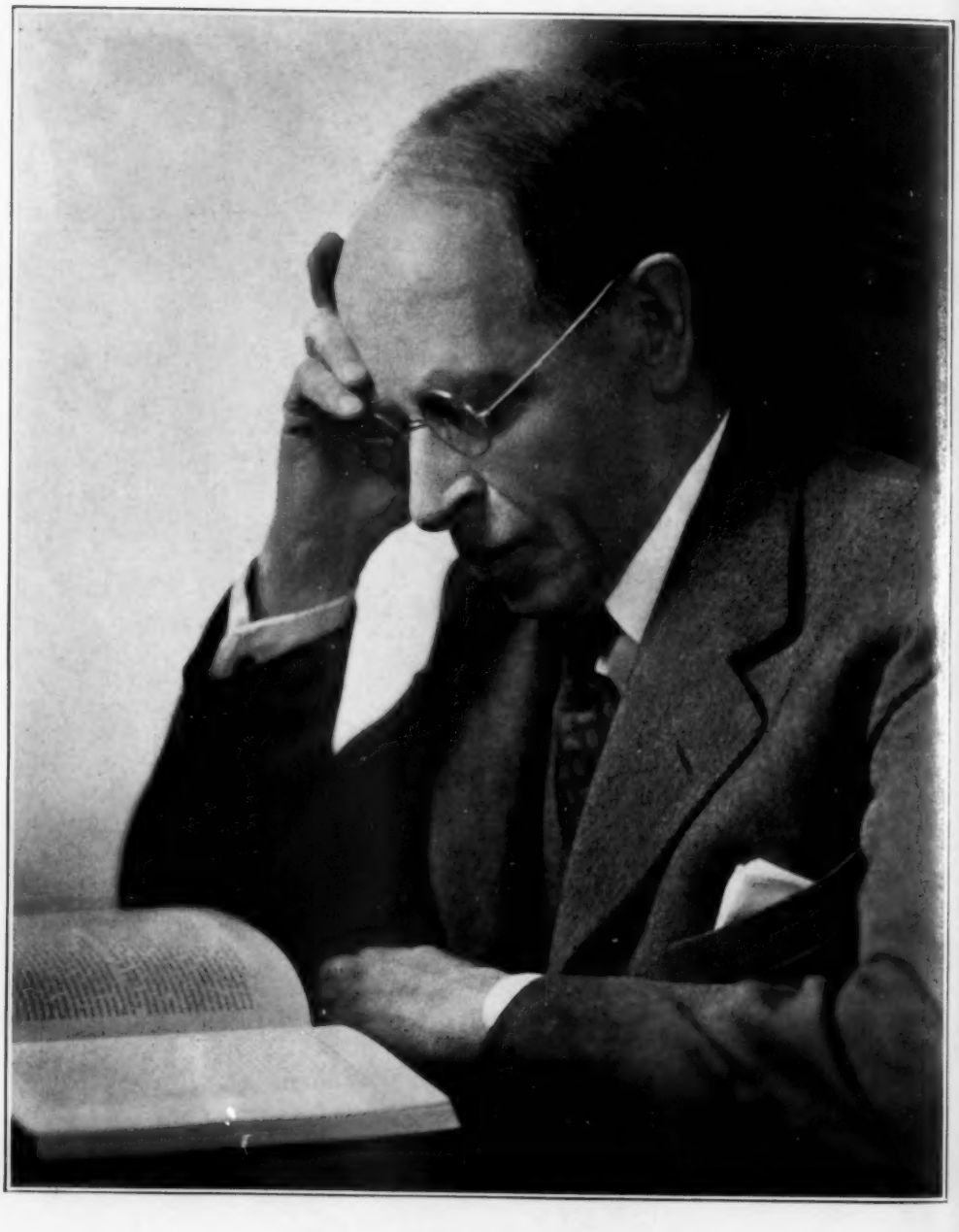
DEDICATED TO

DR. ROBERT BAYLEY OSGOOD

Emeritus Professor of Orthopedic Surgery,
Harvard Medical School

BY

HIS FORMER ASSOCIATES ON THE OCCASION
OF HIS SEVENTIETH BIRTHDAY



Robert B. Osgood.